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SAFEGUARDS IN GASTRIC RESECTION FOR DUODENAL ULCER*

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IT IS the purpose of this communication to present a program of management of the technical aspects of extensive partial gastrectomy for complicated duodenal ulcer that has gradually evolved in this clinic in the four-and-one-half-year period ending January, 1951. As in any teaching surgical service, the training of young surgeons is second in importance only to providing the best possible care for the patient seeking aid in the hospital. Of 200 consecutive resections for duodenal ulcer (including 9 cases of marginal ulcer, which is the same disease but slightly disguised by the altered anatomy resulting from previous inadequate surgery), 104, or 52 per cent, were carried out by members of the resident staff. There were three deaths in the entire group, a mortality rate of 1.5 per cent. This figure of 1.5 per cent can be presented without apology, as it compares favorably with most published series of any size, but certainly without pride, as an autopsy was performed in each of the fatal cases and death was found to have resulted from an ill-advised or poorly performed technical maneuver. One patient died from leakage at the site of a biopsy taken to rule out cancer, one as a result of free leakage from the duodenal stump and one from severance of the pancreatic duct and partial occlusion of the common bile duct by a suture.

MATERIAL

During the period under discussion approximately 900 admissions for the treatment of duodenal ulcer and its complications were recorded at the hospital. Two hundred and forty-one operations were performed for cure of the ulcer in the 236 most severe and intractable cases (Table 1). Thirty-five per cent of the patients admitted for ulcer were operated on. (Because of multiple admissions of some patients this represents about 28 per cent of the hospital admissions for ulcer.)

In view of the recent statistical study of Moore and his co-workers,[1] it is possible that in the future a larger percentage of our patients should be offered the benefits of surgery. In Moore's nonsurgical group the risk of death from late complications of ulcer was approximately equal to the surgical mortality in his operated group (2.9 per cent), whereas the likelihood of a satisfactory long-term result was twice as great in the surgical group, in terms of lack of symptoms and economic usefulness, as in the nonsurgical group.

TABLE 1. *Operations for Cure of Duodenal Ulcer in 236 Patients.*

	No. of Cases	No. of Deaths	Mortality
			%
Gastroenterostomy alone	5	1	20
Vagotomy	36*	0	0
Extensive partial resection	200*	3	1.5
	241	4	1.7

*Five patients fall into both categories; there were 4 vagotomy failures with subsequent resections and 1 resection failure with subsequent vagotomy.

Gastroenterostomy Alone

This procedure will always have a small place in the treatment of elderly, cachectic, poor-risk patients in whom the problem is cicatricial obstruction rather than any current activity of the duodenal ulcer. It can and should be carried out under local anesthesia as a planned procedure in patients who are in imminent danger of death from starvation — and rarely under any other circumstances. In the present series it was carried out 5 times, with 1 death.

Vagotomy

Early in the period under discussion this procedure was carried out in 32 cases. Thirty of these cases were reported by Warren and Meadows[2]; the early results were about equal to those in a somewhat larger group treated by gastric resection.

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Shortly thereafter, however, more and more of these patients were troubled by recurrences and increasing functional disabilities, and the operation was abandoned in favor of resection. A recent survey of these original 32 cases is summarized in Table 2 and shows clearly why the procedure has fallen into disfavor in this hospital. The recurrence rate is almost 30 per cent, with 1 death from recurrent ulcer and other severe functional problems. It should be pointed out that recurrences were highest in the patients having vagotomy alone or vagotomy with pyloroplasty. The recurrence rate after vagotomy and posterior gastroenterostomy was 14 per cent. Therefore, at the present time we believe that vagotomy is indicated only in the case of marginal ulcer, when an adequate resection has been carried out, and the adequacy of resection must include pathological proof that the antrum and pylorus have been removed. Since vagotomy ceased to be an elective procedure it has been used 3 times, combined with gastroenterostomy, when apparently severe technical problems involving the duodenum led to the abandonment of the planned resection.

TABLE 2. *Results of Vagotomy (18-54 Months).*

	VAGOTOMY ALONE	VAGOTOMY WITH DRAINAGE OPERATION	TOTAL NO. OF CASES	PERCENTAGE OF CASES
No. of cases	21	11	32	—
Proved recurrence	5	4	9	28.1
Dead (perforation of recurrent ulcer)	1	0	1	3.1
Dead (unrelated causes)	3	0	3	9.4
Reoperation	2	3	5	15.6
Lost to late follow-up	4	1	5	15.6
Well; no further operation	6	6	12	37.5
Not well; no further operation	2	0	2	6.2

Extensive Partial Gastric Resection

Two hundred and three patients were operated on with the intention of carrying out this procedure. Because of marked obesity, extensive inflammatory masses around the duodenum and poor general condition of the patient, the procedure was abandoned 3 times, as mentioned in the preceding paragraph, giving a resectability rate of 98.5 per cent.[3] Of the 200 resections, 13 were carried out as urgent or emergency procedures for the control of massive bleeding. None of the 3 deaths occurred in this "urgent" group. The remaining cases were carried out as elective, scheduled operations.

General Considerations

In a program based on resection that is adequate in scope, effective and reasonably safe for the resident and senior staffs alike, there are many factors of importance other than the technical problems encountered at the operating table. These factors include the proper selection of cases so that unnecessary surgery is not advised, adequate preparation with diet, aspiration and administration of fluid and blood as the changing conditions demand, the use of the proper time for operation, a competent anesthesiologist and alert postoperative management. The operation itself is but an incident in the over-all surgical care of these patients, but it is the only one that will be emphasized in this presentation. One factor that deserves passing mention is the time of operation. Once the internist, surgeon and patient have agreed that operation is necessary, there is great pressure from the patient and his family to get the operation over with at once. It is certain that a few days to a week or more of the strictest medical management at this time will pay dividends in the reduction of the inflammatory reaction and thereby make the procedure easier for surgeon and patient alike. Ulcer pain is a manifestation of penetration, inflammation and activity of the ulcer, and if the patient can be rendered asymptomatic for even a few days the operation will be easier.

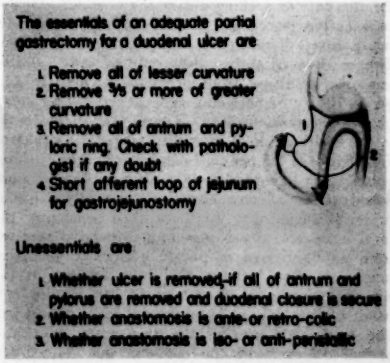

FIGURE 1. *Essential and Unessential Features of Adequate Partial Gastrectomy for Duodenal Ulcer.*

Criteria for Adequate Gastric Resection

There are four essentials for an adequate partial gastric resection (Fig. 1):

The removal of essentially all the lesser curvature. To accomplish this one must resect well above the left gastric artery. This implies that if the clamp were applied any higher it would encroach on the lumen of the esophagus.

The removal of three fifths or more of the greater curvature. To accomplish this one must go at least beyond the first short gastric vessel leading toward the spleen.

The removal of all of the antrum and all of the pyloric ring. This is indubitably the most important single factor. In 1909 Edkins and Tweedy[4] showed that the isolated antrum released a potent stimulant to acid secretion by the fundus; they believed that this was due to a hormone. Dragstedt and others[5] and Schilling and Pearse[6] have more recently demonstrated this important humoral effect resulting from retained antral mucosa leading to excess gastric secretory activity. A number of marginal ulcers that have developed after apparently adequate gastrectomy have been permanently cured by simply removing a small segment of retained antrum and pylorus.[7, 9] The distortion caused by an active ulcer may make it difficult to be certain where pylorus stops and duodenum begins, and it is sometimes necessary to ask the pathologist to prove by frozen section that one has definitely secured a rim of duodenal tissue. The combination of these three steps assures a two-thirds removal of the stomach, — and the amount removed may be as great as four fifths.

The use of a short afferent loop of jejunum, no longer than is necessary to assure lack of tension on the anastomotic suture line.

There are also three unessential factors that have caused surgeons much confusion and distress:

The removal of the ulcer itself. This is not essential — *if both antrum and pylorus are completely removed and the duodenal closure is secure.* An ulcer just distal to the pylorus can always be removed, but the removal of an ulcer well down in the duodenum is fraught with serious danger of damaging the common duct[8] and, what is less often remembered, the pancreatic duct. An ulcer that recurs after gastric resection appears not at the site of the original ulcer but always near the new stoma. Nor does the presence of a retained scar predispose to marginal ulceration. The ulcer or part of it was left behind in 66 of the present series of 200 cases, yet in the 3 marginal recurrences that have so far developed there was histologic proof that the original duodenal ulcer had been excised. There has never been well documented evidence that an *ultrapyloric* exclusion procedure predisposes to marginal ulcer, whereas there is abundant proof that a *prepyloric* exclusion operation strongly predisposes to a marginal recurrence.

Whether the anastomosis is antecolic or retrocolic. If the afferent jejunal loop is brought up well to the left where the transverse colon climbs towards the splenic flexure, the loop can be made within an inch as short as a retrocolic anastomosis. In an antecolic procedure the chance of damaging a colic vessel is obviated, the chance of obstruction from the mesocolon's slipping downward over the jejunal loop is nil, the anastomosis is performed more quickly and easily and any necessary subsequent operation is facilitated. Although the antecolic anastomosis has become our usual maneuver in the last two years, the retrocolic anastomosis is still used, particularly when there is a long "drooping" mesocolon.

Whether anastomosis is isoperistaltic or antiperistaltic. There is always one way of lifting the jejunal loop so that it hangs straight and clear; if one reverses its axis there is more or less of a twist. The position in which it hangs freely is the one in which the anastomosis should be performed, whether it be isoperistaltic or antiperistaltic.

Technical Considerations

The Stomach and Its Anastomosis

In practically all cases the anastomosis of stomach and jejunum is carried out in the manner of Hofmeister, with partial closure of the angle along the lesser curvature. This converts the stomach remnant into a somewhat tubular structure, which allows a shorter jejunal loop to be used and decreases the size of the gastrojejunal lumen. Open anastomosis is performed, with two layers of sutures, the inner of fine catgut for hemostasis, the outer of Halsted mattress sutures of silk or cotton through the seromuscular layers. Enterostomy clamps are not used because they obscure bleeding points that should be individually ligated and because they may also contribute to the development of postoperative edema around the stoma. Special clamps are not necessary; in fact, large crushing clamps are to be avoided. Three pairs of narrow, straight, well-fitting Kocher clamps are all that is needed to remove the stomach, and no clamps at all are used on the jejunum. The upper part of the resection and the anastomosis are routine, if sometimes bloody and tedious, surgical exercises. The vascularity of the stomach remnant and the jejunum assures rapid and solid healing of the anastomosis.

The Duodenum and Its Closure

It is axiomatic in surgery for duodenal ulcer that the major complications and the mortality depend on how the duodenum is handled and what happens to the duodenal stump after operation. There are three general groups of problems; these will be discussed in turn.

The easy or "routine" duodenum. This group includes the cases in which the ulcer is near the pylorus and neither too big nor too active. It also includes the much smaller number of cases in which the ulcer is well down in the duodenum, with plenty of normal duodenum beyond the pylorus, but proximal to the ulcer itself (Fig. 4*A*). After rather straightforward dissection, clamps can be placed across normal tissue distal to the pylorus and clear of the indurated tissues around the ulcer. Normal duodenum covered with serosa both anteriorly and

posteriorly is found, and the stump can be closed with a single over-and-over suture of fine catgut and then infolded with a seromuscular row of Halsted mattress sutures of fine silk or cotton. If the margin of normal tissue is less than one would wish, it is best to divide the duodenum with no clamp on the distal open end, ligate any bleeding vessels and turn the end in with a simple row of seromuscular mattress sutures. *A single row of well placed nonabsorbable mattress sutures that bring the seromuscular layers together without tension is infinitely safer than multiple rows of sutures that are too tight.*

FIGURE 2. *Two-Stage Gastrectomy: the First Stage. The small clamps depicted along the lesser curvature represent full-sized Kocher clamps; they are not special clamps. (Their disproportionate size is the result of inaccurate instructions given to the artist.)*

The duodenum that is obscured and distorted by marked inflammatory reaction around a penetrating ulcer. In such cases there may be a large inflammatory mass involving the pylorus, the duodenum and the head of the pancreas; there may even be local abscesses from penetration into the hepatoduodenal ligament or under the liver edge. In such cases the dissection of the duodenum may be extraordinarily difficult because of adhesions and bleeding, and when one finally dissects beyond the ulcer he may find that the tissues are inadequate for closure or that the common duct is very close to the margin of the dissection. Therefore, it is our policy, whenever an unusually large inflammatory mass presents, to carry out a two-stage resection (Fig. 2 and 3). This procedure has been well described by McKittrick[9] and endorsed by Allen[10] and others.[11] In essence, the stomach is deliberately divided through the antrum well proximal to the pylorus (Fig. 2*A*), the ulcer mass is left behind, the antrum is closed in on itself (Fig. 2*B* and 2*C*) and an adequate partial gastrectomy is carried out with establishment of the gastrojejunal anastomosis. Decision to carry out this two-stage procedure must be made promptly, before dissection down toward the pylorus has resulted in division of the right gastric and gastroepiploic vessels at such levels that the antral segment is devascularized and cannot be closed on itself. Secondly, one must leave plenty of antrum for easy closure of normal tissues. Finally, one should not biopsy the inflammatory mass. This procedure was carried out in one case in the present series in order to rule out cancer and resulted in death from a leak at the site of the biopsy.

FIGURE 3. *Two-Stage Gastrectomy: the Second Stage, Six Weeks Later, — Removal of Antrum and Pylorus. Insert shows completed resection.*

The second stage is carried out approximately six weeks later; the retained antrum and pylorus are removed (Fig. 3). By this time there will have been an extraordinary resolution of the inflammatory process; the indurated inflammatory mass is represented by scar tissue only, — and sometimes by very little of that. Furthermore, the patient will have been at home for a month and the function

of his gastrojejunostomy will have been well established. The anastomosis is not touched at the second stage, and if there is any difficulty with the closure of the duodenal stump at this time one knows that there is no chance of back pressure on it from edema around the afferent limb of the gastrojejunal anastomosis.

This two-stage gastrectomy was carried out in 18, or 9 per cent, of the present series. As one's experience increases this procedure will be used on fewer occasions, but there will always be an occasional case in which it transforms a surgeon's nightmare into a routine, if interrupted, operation. It was undoubtedly the frequent use of this procedure

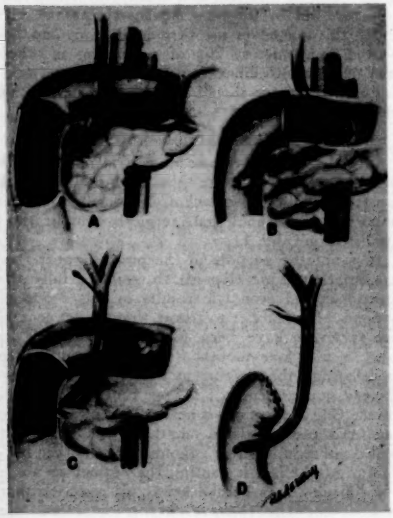

FIGURE 4. *Protection of the Common Bile Duct.*

that kept the mortality in the present series at the reasonable level of 1.5 per cent.

This procedure has a major drawback in that it requires a second hospitalization and operation, but its safety and ease more than compensate for this. It is important that all patients be apprised of the possibility of a two-stage operation, as the decision is never made until the operation is under way, — and if the patients have already been told that this may be done for their own safety they are appreciative rather than confused and unhappy when they learn that a second procedure is contemplated. If the second stage is postponed too long a marginal ulcer is likely to develop because of the hormonal activity of the retained antral mucosa, although in no case in the present series was the second stage so long postponed. If this should occur, the marginal ulcer needs no treatment other than the resection of the antrum and pylorus, the *duodenal* ulcer is not reactivated and the technical problems of the second stage are not increased.

We have found no place for the Finsterer *prepyloric* exclusion procedure with excision of the antral mucosa. This procedure is difficult and bloody; one can never be certain that all the mucosa is removed; one is left with a thinned-out seromuscular shell that is unsatisfactory for secure closure; and there is a suspicion that the pyloric muscle may, like the antral mucosa, stimulate the formation of a marginal ulcer.

The two-stage resection can be used even when there is an obstructive element in the duodenal

FIGURE 5. *Inadequate Posterior Duodenal Wall: a Method of Closure.*

ulcer; there has been no blow-out of the retained antral segment in our series or McKittrick's[9] because of obstruction at or beyond the pylorus.

The duodenum that is distorted from scarring in long-standing ulcer. In certain cases, particularly in long-standing ulcer with intermittent activity and healing, scar tissue causes foreshortening of the first and second portion of the duodenum and may involve the duodenal end of the hepatoduodenal ligament to such a degree that the common duct is drawn over toward the area of the ulcer (Fig. 4*B*). When scarring, rather than actual inflamma-

tion, is the primary factor causing the distortion, the two-stage procedure is not helpful; scar tissue will not melt away in the interim as inflammatory tissue does. When scarring is extensive, particularly along the upper curve of the duodenum, the common duct must be visualized. Usually, if one keeps the superior dissection close to the wall of the duodenum one will penetrate the scarred area and the common duct will then retract down and laterally out of harm's way. However, if the scarring is especially dense in this area the common duct is best protected by opening it higher and introducing a probe or a woven bougie through it into the duodenum (Fig. 4*C*). This affords positive identification of the common duct throughout its length and enables one to dissect without damaging this vital structure and to close the duodenum without impinging on the ampulla (Fig. 4*D*). When the common duct is opened, as was done in 5, or 2.5 per cent, of the series, a T-tube is introduced for temporary drainage at the end of the operation.[8]

Scar tissue or the bed of an active ulcer may completely replace the posterior wall of the first portion of the duodenum (Fig. 5*A*). In such cases the duodenum should be divided obliquely, conserving the normal tissues of the anterior wall. The stump can then be closed by rolling the anterior wall over on itself, abutting the seromuscular layers of the anterior wall against the muscularis that remains posteriorly and suturing the pancreatic bed and capsule to the normal tissues of the anterior wall with a second row of sutures[11, 12] (Fig. 5*B*).

In any case where there is any doubt concerning the security of the closure of the stump, it is good practice to thread the Levine tube through the gastrojejunal anastomosis into the afferent (duodenal) loop and to place a large drain near but not touching the duodenal stump (Fig. 5*C*). These maneuvers ensure that there will be no back pressure against the closure; furthermore, if there is any leakage from the stump the juices can escape along the drain, forming a temporary external fistula rather than leaking into the peritoneal cavity. These last two maneuvers were used 10 times in the present series.

Finally, the surgeon must be acquainted with the maneuver described by Welch,[13] for use in the very rare case in which it is impossible to close the duodenum. This consists of passing a catheter through the open end of the duodenum and simultaneously preparing a catheter jejunostomy in the efferent jejunal loop. Such a catheter duodenostomy sets up a controlled duodenal fistula; the secretions can be collected and reintroduced through the jejunostomy if they are of significant volume. After the gastrojejunal anastomosis is functioning well, the duodenostomy catheter can be withdrawn in a week or so and the fistula will soon close. Interestingly enough, it was not necessary to do this in any case in the four-and-a-half-year series here reported, but in the four months since the series ended this maneuver has been used twice and has proved a satisfactory way of controlling an otherwise desperate technical impasse. Anyone performing gastric surgery should read Welch's description of this technic.

Table 3. *Nonfatal Surgical Complications of Gastric Resection in 200 Cases.*

	No. of Cases	Percentage of Cases
Intraperitoneal abscess	6	3
Common-duct obstruction*	1	0.5
Pancreatic cyst*	1	0.5
Hemorrhage†	2	1
Duodenal fistula	2	1
Temporary stomal obstruction‡	8	4
Wound infection	19	9.5
Dehiscence	1	0.5
Thromboembolism	5	2.5
Incisional hernia	7	3.5
Homologous hepatitis	2	1.0
Hydropneumothorax	1	0.5

*Required operation.
†Operation required in 1 case.
‡Did not require operation.

Surgical Complications and Results

In 200 consecutive cases of gastric resection for duodenal ulcer there were three deaths, all of which must be attributed to technical difficulties. Other important but nonlethal surgical complications are listed in Table 3.

It is not the purpose of the present paper (nor has sufficient time elapsed) to evaluate fully the functional and economic results in this group of patients. It is proper to report that 87 per cent of the survivors have been followed for periods of four to fifty-four months (average, twenty-three months) and three recurrent ulcers have been discovered, an incidence of 1.7 per cent of those followed. One of these ulcers healed after transthoracic vagotomy performed ten months ago; another had healed six months after vagotomy at another hospital; and the last is causing the patient so much less difficulty than he had before his resection that he does not wish to have another operation. He controls his condition by diet and is able to work regularly, whereas previously he was physically and economically incapacitated by intractable pain.

Summary

A method of gastric resection for duodenal ulcer that was found to be applicable to 98.5 per cent of a series of cases selected for operation is presented. This plan was found effective and relatively safe in the hands of both the senior and resident staffs, with a mortality rate of 1.5 per cent.

The poor results of vagotomy in this clinic are enumerated and the essential and unessential factors in adequate gastric resection are listed and discussed.

Various technical aspects of dealing with the duodenum are described, with special emphasis on

the important role of the two-stage procedure. Methods for protecting the common duct and the closure of the duodenal stump are reviewed.

The results and surgical complications are enumerated.

No claim to originality is made in this program, which includes the methods of many teachers and authorities modified by experience at this clinic.

Conclusion

Extensive partial gastrectomy is a potent and relatively safe technic for treatment of complicated duodenal ulcer if certain criteria are met and full use is made of various surgical safeguards.

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ACTH THERAPY IN ULCERATIVE COLITIS AND REGIONAL ENTERITIS*

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BOSTON

THE purpose of this communication is to evaluate the clinical use of ACTH in nonspecific ulcerative colitis and regional enteritis. The immediate and long-term effects of this treatment on the clinical course of 6 patients with ulcerative colitis and 2 patients with regional enteritis have been studied over a period of sixteen months, and the response to ACTH therapy was correlated with the fecal lysozyme titer, which is a measure of the activity of the disease.

The rationale of this use of ACTH is based upon its beneficial effect on systemic diseases involving mesenchymal tissue or in which an antigen-antibody reaction may be involved. Moreover, the occurrence of polyarthritis in ulcerative colitis and its relation to chronic stress offered further incentive to the study.

Selection of Patients

Since spontaneous remissions may occur in these diseases, only patients with severe intractable ulcerative colitis in the acute phase were selected for treatment. All these patients were markedly incapacitated and had not responded to an adequate control period (one to four months) of good medical management that included antibiotics, detergents, prolonged bed rest, diet, blood transfusions and the usual supportive therapy. Two patients had received psychotherapy as part of the medical regimen.

The activity of the disease was reflected by fever, leukocytosis, anemia, anorexia, profound weight loss, abdominal pain, tenesmus and intractable bloody diarrhea (8 to 15 evacuations daily). The sigmoidoscopic examination demonstrated a diffusely ulcerated, freely bleeding, friable mucosa and the roentgen studies revealed extensive involvement of the colon and rectum.

The patients with regional enteritis were completely invalided and presented the characteristic picture of the disease on x-ray examination.

Treatment

The psychologic effects of a new form of treatment were minimized whenever possible. The patients were given placebos parenterally in many instances before ACTH therapy was begun and were not informed of the change in medication. A moderately unrestricted, bland diet was maintained unaltered through the control and treatment periods. All medication except phenobarbital was discontinued during the period of study.

ACTH¶ was administered in doses of 20 to 40 mg. intramuscularly at six-hour intervals for periods of four to eight weeks, depending on the requirements and clinical response of the individual patient. At the end of treatment the dose was reduced gradually over a period of five to seven days. All patients were

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¶Supplied by Dr. John R. Mote of the Laboratories of the Armour Packing Company.

maintained on a limited salt and fluid intake and were given 0.9 gm. of potassium chloride three times daily.

Two patients were treated orally with cortisone during a relapse after ACTH therapy. They received 100 to 125 mg. twice daily for ten to twenty-one days.

Laboratory studies included the blood eosinophil count,[1] urinary 17-ketosteroids and sedimentation rate, serum proteins, fasting blood sugar, blood carbon dioxide, serum chlorides, hematocrit, hemoglobin and white-cell count.

The consistence, appearance and number of stools were recorded daily and the stools were analyzed for occult blood. The appearance of the colon was studied by repeated proctosigmoidoscopic and barium-enema examinations. The fecal lysozyme titer[2] was determined at frequent intervals prior to, during and after ACTH therapy.

Results

Ulcerative Colitis

Five of the 6 patients with ulcerative colitis who were treated with ACTH during the acute phase of the disease experienced a definite and often dramatic remission. The unrelenting diarrhea that had persisted for months in spite of previous therapy decreased significantly within the first week of treatment and was usually brought under control within two weeks. There was an accompanying diminution or disappearance of blood in the stools, with marked relief of abdominal pain and tenesmus (Table 1).

The characteristic euphoria and increase in appetite resulting from ACTH administration were noted in the successfully treated patients soon after therapy was started and were associated with a prompt disappearance of fever and a fall in the sedimentation rate and the fecal lysozyme titer.

There appeared to be a lag between the clinical improvement, which occurred within two weeks of treatment, and the objective evidence of healing on sigmoidoscopic examination, which required three to four weeks.

The dramatic response to ACTH therapy is demonstrated by the following case history (Fig. 1):

Case Report

Case 1. O. D., a 46-year-old man, complained of fecal incontinence, — particularly nocturnal diarrhea, — of 4 months'

Table 1. *Clinical Data of ACTH Therapy in Ulcerative Colitis.*

Patient	Dosage of ACTH	Days of Treatment	Duration of Diarrhea	Duration of Gross Blood in Stools	Proctoscopic Improvement (Days After Treatment)	Systemic Improvement	Remission		Relapse
							Duration	Weight Gain	
	mg./day		*days*	*days*				*lb.*	
E. G.	80	18	6	6	22	4+	2 months	10	Severe
	200*	14	21	21	0	0			
	50*	7							
	120	14	2	33	30	2-3+	2 weeks	0	Severe
	40	19		(trace)					
	250*	21							
	150*	7	7	40		2-3+	4 weeks	12	None
	100*	7		(occasional)					
	75*	14		trace)					
O. D.	100	24	7-10	7-10	21	4+	16 months	40	None
	40	18							
B. F.	100	21	12-14	14	17	4+	9 months	30	Mild
	250*	10	10	8-10	30	3+	1 month	10	None
A. M.	80	24	10-12	12-14	21	3-4+	4 months	25	Moderate
	100	16	7-10	7-10	25	4+	8 months	10	
O. H.	80	11	11	11		2+			
	160	22	9	12					
	80	7			30	3-4+	2 months	17	None
	40	7							
L. B.	100	15							
	200*	14	29	29	No change	None	None	None	Ileostomy

* Cortisone.

Case 1. O. D., a 46-year-old man, complained of fecal incontinence, — particularly nocturnal diarrhea, — of 4 months' duration, with 10 to 18 blood-stained watery evacuations daily, associated with marked tenesmus, abdominal pain, a low-grade fever, generalized joint pains and a 25-lb. weight loss. This patient had been hospitalized for 4 months previously and had not responded to intensive medical therapy, including the use of antibiotics, detergents and psychotherapy. Within 1 week of ACTH treatment (100 mg. daily) the number of evacuations decreased to 5 semi-formed stools daily, and by the end of the second week the patient was passing 1 to 3 formed stools daily that were free of occult blood. This was the first time in 4 months that a formed stool was observed. The joint pains disappeared completely.

The control of diarrhea was accompanied by a marked diminution in the abdominal pain and tenesmus within the first week of treatment, with complete disappearance of these symptoms by the end of the second week. Marked euphoria and increase in appetite were noted soon after therapy was begun, with a resultant gain of 10 lb. within 1 month. The clinical remission was paralleled by a prompt fall in sedimentation rate and fecal lysozyme titer and a rise in the hematocrit.

A similar, though sometimes less dramatic, response to treatment was observed in 4 additional patients with severe, previously intractable ulcerative colitis. Although the diarrhea did not disappear completely in every case, there was a marked diminution in the daily number of stools and a

significant change in the consistence, so that the patients were passing 2 to 3 formed or semi-formed stools daily within two weeks of treatment.

The only patient who failed to respond to fifteen days' treatment with ACTH and two weeks of cortisone therapy had a twenty-three-year history

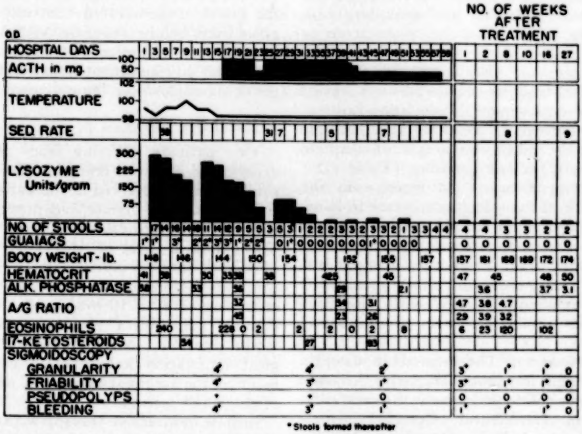

FIGURE 1. *Effects of ACTH on Ulcerative Colitis.*

and diffuse ulceration were, in some cases, spectacularly decreased. In one patient the mucosa appeared essentially normal except for evidence of fine granularity after three weeks of treatment (E. G.). In no instance, however, did the mucosa completely revert to normal within this period.

of the disease, with extensive fibrosis and cicatrization of the entire colon, multiple strictures and perianal and perineal fistulas (L. B.).

Blood loss. Gross blood in the stools usually disappeared and the occult blood diminished significantly within two weeks of treatment. In 2 patients with ulcerative colitis in whom gross blood had been observed consistently for three to four months, the stools became free of occult blood within ten days of ACTH therapy (O. D. and E. G.). Persistent occult blood in the stools was observed, however, for two to four months after treatment in several patients (B. F. and O. H.) and presented a serious problem in one patient (A. M.) with polyps in the transverse colon. Patient E. G. required multiple blood transfusions because of persistent blood loss for eight weeks after ACTH and cortisone treatment for a severe relapse.

Sigmoidoscopic appearance. Definite and sometimes dramatic evidence of remission was observed by sigmoidoscopy, but there was usually little or no improvement in the mucosal appearance until after three weeks of therapy. The lag between the clinical and the sigmoidoscopic reflections of the disease process was observed consistently.

The mucosa was distinctly less friable and granularity was markedly diminished. Pinpoint bleeding

Marked improvement was observed in O. D. (Fig. 1) after three weeks of treatment, although minor residual granularity and bleeding were still present. A small single inflammatory pseudopolyp

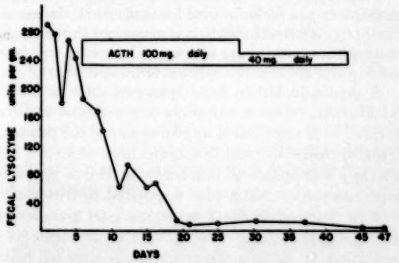

FIGURE 2. *Effect of ACTH on Fecal Lysozyme.*

seen on two occasions in the rectal mucosa disappeared within three weeks. Six months later the mucosa was indistinguishable from normal.

Less marked but definite improvement was observed in patients B. F. and A. M. after a similar

period of ACTH therapy. In addition to the mucosal improvement (Patient B. F.), a draining painful perianal fistula 10 mm. in diameter had decreased to 6 mm. and was no longer inflamed. The fistula diminished to 2 mm. in diameter, and further improvement in the sigmoidoscopic appearance was observed three weeks after treatment was discontinued, although the rectal mucosa was still moderately friable and granular, with pinpoint bleeding.

A stricture noted during the examination of Patient A. M. persisted after treatment, although it appeared considerably less edematous.

There was no improvement in the appearance of the mucosa of Patient L. B., who had multiple strictures, polyposis and fistulas, in spite of adequate treatment with ACTH and cortisone (Table 1).

Roentgenologic appearance. An increase in the caliber and length of the colon, an increase in haustral markings and a more normal mucosal pattern were demonstrated in 3 patients after treatment (B. F., A. M., and O. D.). There were no significant changes in the roentgenographic appearance of the colon in the remaining patients with ulcerative colitis, except for some diminution of spasm and irritability.

Systemic improvement. The intractable anorexia and persistent weight loss that characterize the acute phase of ulcerative colitis and present the most difficult challenge in management responded impressively to treatment. ACTH uniformly produced a consistent and impressive increase in the appetite and sense of well-being. This was usually the first clinical evidence of remission and was accompanied by disappearance of fever and a fall in the sedimentation rate within a few days of therapy. Increases in the hematocrit, plasma proteins and body weight were observed later in the course of treatment.

Fecal lysozyme. Lysozyme, a mucolytic enzyme present in the colonic mucosa and other tissues in the body, is found in high concentrations in the stools during the acute phase of ulcerative colitis and falls during the chronic-inactive or remission phase.[3, 4]

A profound fall in fecal lysozyme titer occurred within four to seventeen days of treatment and coincided with the clinical improvement of the patient. This decrease in fecal lysozyme titer after ACTH therapy was observed uniformly in the 5 patients with ulcerative colitis who responded to treatment.

The decrease in fecal lysozyme titer paralleling the clinical course of the disease is demonstrated in Patient O. D. (Fig. 2), in whom the titer fell from the pretreatment levels of 291 units per gm. to the chronic inactive level of 7 units on the twentieth day of ACTH treatment and has remained below 5 units for sixteen months. Similarly dramatic decreases in fecal lysozyme titer were observed in all other patients with ulcerative colitis who experienced a remission on ACTH treatment. The effect of ACTH on fecal lysozyme will be reported elsewhere in more detail.[5]

Patients completely incapacitated by extensive cicatrization of the bowel may demonstrate normal or only mildly elevated lysozyme titers, since these patients evidently possess insufficient actively functioning colonic mucosa to secrete increased lysozyme. Patient L. B., for example, with extensive fibrosis of the bowel, demonstrated relatively low fecal lysozyme titers before treatment with ACTH and cortisone, in spite of the activity of the disease process. There was no consequent lysozyme fall and no clinical or sigmoidoscopic improvement.

Regional Enteritis

Two patients suffering from regional enteritis experienced a definite remission after ACTH therapy similar to that observed in the patients with ulcerative colitis. The disease had proved intractable to long periods of medical management in both patients. The dramatic effect of ACTH on the acute phase of regional enteritis is demonstrated by Patient I. N., who was hospitalized because of watery diarrhea consisting of 8 to 10 evacuations daily, severe abdominal pain and a 35-pound weight loss of ten weeks' duration. X-ray studies and a previous surgical exploration had revealed extensive involvement of the terminal ileum and multiple segments of the small intestine.

In spite of intensive therapy with antibiotics, diet, blood transfusions, parenterally administered fluids and sedation, the patient's course was progressively downhill. Weight loss, severe intractable cramping abdominal pain, nausea and vomiting continued in spite of treatment. The abdominal examination revealed diffuse tenderness and involuntary rigidity.

Within the first three to four days of treatment with ACTH, the previously intractable abdominal pain was relieved and the stools became formed for the first time in three months. The patient developed a sense of well-being and his appetite became ravenous. Within three weeks he gained 27 pounds and averaged 2 formed bowel movements daily, free of occult blood.

Although a marked decrease in intestinal motility and spasm was observed in both patients by roentgenographic examination, the disease process in the ileum and other portions of the small intestine did not appear altered by ACTH therapy.

Long-Term Follow-Up

In all but 2 patients, definite relapses occurred within two to nine months after the discontinuation of ACTH therapy. The relapses were less severe in all but one patient (E. G.) and responded to a second course of ACTH or cortisone therapy.

Patient A. M. had been bedridden for five months prior to therapy because of intractable bloody diarrhea, tenesmus, 30-pound weight loss, arthritis and draining pyoderma gangrenosum of the legs. She

responded satisfactorily to three weeks of ACTH treatment (80 mg. daily). A recurrence of the diarrhea, with gross blood, occurred four months later, however. The colitis responded again to sixteen days of ACTH therapy (100 mg. daily). The patient has remained essentially asymptomatic, without further relapse, for eight months and has gained 35 pounds in weight. Anemia and occult blood in the stools have persisted, however, presumably because of polyps in the transverse colon demonstrated by x-ray. Proctoscopy reveals a healed, inactive ulcerative colitis, with some thickening of the mucosa and fine granularity but no friability or gross bleeding.

A mild relapse occurred in another patient, B. F., nine months after ACTH therapy. Although there were transient episodes of diarrhea after dietary indiscretions during this period, the patient had gained 25 pounds and sigmoidoscopy revealed a thickened, healed, slightly friable, finely granular mucous membrane and a small persistent fistula. The patient was treated at home with 125 mg. of cortisone given orally twice daily for ten days and had a prompt remission. Proctoscopic examination after the second course of therapy revealed slight thickening of the mucosa but no evidence of active ulcerative colitis.

A very severe relapse after prolonged physical exertion occurred two months after ACTH treatment was discontinued in patient E. G., who had previously experienced an excellent and dramatic response to ACTH therapy. A course of cortisone, 200 mg. a day for fourteen days, followed by 120 mg. of ACTH daily for fourteen days, resulted in some improvement. The patient was then maintained on 40 mg. of ACTH daily for an additional period of nineteen days. Two weeks after ACTH was discontinued, the patient experienced another severe relapse, which responded dramatically to cortisone therapy (125 mg. twice daily given orally for three weeks, followed by gradually reduced doses over a period of six weeks).

A 29-year-old man who was incapacitated for six months by bloody diarrhea (eight to ten times daily) had a satisfactory remission that has persisted for two months after therapy. The patient is now able to work every day and has gained seventeen pounds, although he has three to four semi-formed stools daily. Insufficient time has elapsed to evaluate the permanency of the remission.

A continued remission for sixteen months has been observed in one patient who is being maintained on a full, unrestricted diet. This patient works regularly, has gained 40 pounds and presents an essentially normal rectal mucosa on proctoscopic examination, although the x-ray studies reveal residual narrowing, shortening and lack of haustration of the colon. This man had been completely incapacitated for seven months prior to treatment.

Both patients with regional enteritis had mild recurrences of diarrhea one month after ACTH was discontinued. Patient I. N. was given a second course of ACTH therapy and responded promptly, with an excellent remission and a weight gain of 30 pounds. A second relapse occurred, however, as soon as the ACTH was discontinued.

Discussion

Any evaluation of therapy in ulcerative colitis and regional enteritis must take into consideration the spontaneous remissions that occur in these diseases. In view of the selection of patients and the control periods of observation, however, these studies indicate that ACTH is capable of inducing a remission or accelerating its appearance in patients who are incapacitated by the disease and are refractory to other forms of medical management.

The frequent relapses observed two to nine months after discontinuation of therapy and the persistence of occult blood in the stools associated with some residual evidence of activity on sigmoidoscopic examination emphasize the fact that ACTH does not cure the disease.

Although the dramatic effect obtained in one patient who has remained in a constant remission for sixteen months is encouraging, similar remissions may occur spontaneously without specific treatment.

The best therapeutic effect of ACTH has been seen in the early stages of the disease, before complications of stricture, polyps and fistulas occur, although patients B. F. and A. M. experienced a satisfactory remission in spite of these difficulties. No remission may be anticipated in patients with diffuse cicatrization and extensive fibrosis.

The sense of well-being and increase in appetite, which are among the most dramatic effects of ACTH, are of inestimable value in the management of these debilitated and malnourished patients. The transition from intractable anorexia to a ravenous appetite often indicates the turning point in the course of the disease. The increased appetite may be the result of an increase in the gastric secretion of acid and pepsin[6, 7] or of the diminution in the systemic manifestations of infection resulting from ACTH administration.

When relapses occurred, the patients in general responded well to a second or third course of therapy. The rationale for long-term maintenance therapy or repeated courses of treatment is demonstrated by the following case:

Case 2. E. G., a 17-year-old schoolboy, a long-distance runner, was admitted to the hospital on June 25, 1950, because of diarrhea, consisting of 10 to 12 watery, blood-tinged or grossly bloody stools, of 4 months' duration. Diarrhea and blood loss were aggravated by strenuous exercise and stress associated with his racing activities and were accompanied by abdominal distress, tenesmus and a 10-lb weight loss. Previous medical management did not appear to alter the severity of the diarrhea or the abdominal distress.

Physical examination revealed no abnormalities except for evidence of weight loss and dehydration. The hematocrit was 43 per cent, the serum albumin 3.9 gm. and the globulin 2.1 gm. per 100 cc., the corrected sedimentation rate 21 mm. per hour, the eosinophil count 756 per cu. mm. and the urinary

17-ketosteroid excretion 9.1 mg. in 24 hours. The stools contained gross blood and revealed no enteric pathogens on culture. The fecal lysozyme titer was 86 units per gm.

Proctoscopy revealed a markedly friable, ulcerated, coarsely granular rectal mucosa with pinpoint bleeding throughout. The patient was placed on a regular hospital diet for 7 days, during which time the diarrhea and gross blood persisted.

ACTH, 20 mg. every 6 hours, was begun on the 7th hospital day, and the patient was treated for 18 days, with a gradual diminution in the dose for the following 3 days. Within 24 hours the stool frequency diminished to 2 daily. Grossly visible blood disappeared on the 6th day of treatment, and the stools became formed for the first time in 3 months. On the 13th day of therapy the stools became guaiac negative. ACTH was the only medication administered and induced the usual eosinopenia to 19 eosinophils per cu. mm. within 3 days and urinary 17-ketosteroid increase to 20.9 mg. per 24 hours within 7 days. The sedimentation rate fell to 12 in one week and the fecal lysozyme decreased to 4.0 units per gm. within 2 days of ACTH therapy.

The patient showed marked euphoria and a ravenous appetite and gained 5 lb. in 2 weeks. He was discharged on July 22 with 1 to 2 formed evacuations daily that were free of occult blood. On the day of discharge the rectal and sigmoid mucosa was indistinguishable from normal.

After discharge, the patient did well except for occasional slight rectal bleeding following extensive exertion. His appetite remained good and he continued to gain weight. In the middle of September, 1950, the patient began training again for long-distance cross-country running. Three days later he again noticed the onset of severe diarrhea and bleeding, with 6 to 7 watery bowel movements daily containing gross blood, associated with marked anorexia, fatigue and lower-abdominal pain. On October 3 he noticed fever of 102°F. and was readmitted to the hospital on October 4, 1950.

On admission the patient weighed 94 pounds, appeared acutely ill and had fever varying from 100° to 102°F. Physical examination revealed abdominal tenderness in both the right and left lower quadrants. On proctoscopic examination a diffusely granular, ulcerated, freely bleeding, very friable mucous membrane was observed. Free blood gushed from the mucosa and obscured the field at frequent intervals. The hematocrit was 34 per cent and the sedimentation rate 33 mm. per hour. The white-cell count was 18,600.

Two hundred mg. of cortisone was administered daily in divided doses for 14 days (October 4 to 18) and then gradually tapered off to 25 mg. daily during the subsequent 6 days. During this period the patient continued to have fever to 100°F. daily, his anorexia and diarrhea persisted and he continued to lose weight, so that on October 17 his weight had decreased to 90 lb. and the hematocrit continued to fall to 29 per cent in spite of an adequate eosinophil response.

ACTH was begun on October 18, the patient receiving 80 mg. daily in 4 divided doses for 4 days and 120 mg. a day for 10 days; this was then tapered off to 40 mg. daily.

The characteristic sense of well-being, increased appetite, decrease in the number of stools and prompt fall in temperature did not occur until the dose was increased to 120 mg. a day, after which remission occurred promptly. After 5 days of the increased dose of ACTH the patient felt exceedingly well, remained afebrile and passed 3 formed and semi-formed evacuations daily, all containing occult blood.

The patient continued to improve with ACTH administration, regained the weight he had lost during the first part of his hospitalization and was discharged on November 5 weighing 95 pounds. The hematocrit on discharge was 34 per cent, and the stools were consistently positive for occult blood.

Proctoscopic examination on November 5 revealed considerable improvement in the appearance of the mucosa. The lower 4 inches of the rectal mucosa appeared almost normal. There was some fine granularity but no bleeding or friability. At the junction of the rectum and sigmoid, on the right lateral wall, the mucosa was hyperemic and very friable and bled profusely on trauma. This was localized to an area approximately 1 inch in diameter. It was thought, however, that this patient's improvement had been generally excellent in view of the fulminating course of the disease.

The patient continued to receive 40 mg. of ACTH daily in divided doses until November 21 and continued to improve during treatment. He had 3 to 4 semi-formed evacuations daily without gross blood, and his hematocrit rose to 38 per cent.

ACTH was stopped on November 21. The patient continued to do well until December 5, at which time he began to have severe diarrhea, — 5 to 6 watery bowel movements a day, — with profuse bleeding of gross blood. In spite of 3 transfusions and Chloromycetin therapy, the patient continued to fail, and his hematocrit on December 19 was 29 per cent. He suffered from almost complete anorexia, and by December 26 his weight had fallen to 85 lb.

The patient refused hospitalization, and on December 26 oral administration of cortisone, 250 mg. daily in 2 divided doses, was begun. On January 2, 1951, he noted a marked decrease in diarrhea and blood loss and an increase in appetite. He continued to improve, and on January 16 the dose of cortisone was decreased to 150 mg. daily. His appetite improved tremendously, and he gained 10 lb. from December 26 to January 16. He was passing 2 to 3 formed or semi-formed stools daily without gross blood, had no abdominal distress whatever and appeared to be progressing satisfactorily.

The cortisone was reduced further to 100 mg. daily on January 23, and the stools became formed by January 30; the patient's appetite remained excellent. The patient was then maintained on 75 mg. of cortisone daily. He continued to gain weight, — a total increase of 15 lb. in 6 weeks, — and passed 2 to 3 formed stools daily containing occult blood. The hematocrit on February 13, 1951, was 38 per cent. Proctoscopy revealed hyperemia and very fine granularity of the mucosa but no friability or gross bleeding.

ACTH appears to offer an additional supportive measure in the preparation of patients for ileostomy. Ileostomy was considered in the patient described above during his second and third relapses. The control of diarrhea, blood loss and intractable anorexia by ACTH obviated the necessity of operation but indicated that the patient was a considerably better risk for this procedure as a result of this treatment.

Dosage and duration of treatment are extremely important factors in the eventual clinical outcome. The longest remission was observed in Patient O. D., who was treated for forty-two days (Table 1 and Fig. 1); the shortest remission and the most severe relapse were experienced by Patient E. G., who received treatment for only eighteen days (Table 2). The optimum period of therapy is probably three to six weeks, with daily doses of 80 to 160 mg., depending on the condition of the individual patient.*

The dose requirement does not appear to be related to the age or weight of the patient or to the severity of the disease. In some cases there was no demonstrable clinical response to 80-100 mg. of ACTH daily, although the eosinophil fall and urinary 17-ketosteroid responses were satisfactory. When the dose was increased to 120-160 mg. daily the clinical effect was immediately apparent (O. H.). The final decision concerning dosage and duration of therapy depends on the clinical response.

The complications of ACTH therapy consisted of a temporary increase in the fasting blood sugar to 300 mg. per 100 cc. in 1 patient (A. M., Table 1) within two weeks of ACTH administration, with return to normal levels fourteen days after the medication was discontinued. This patient also developed sterile subcutaneous abscesses, a virus pneumonia, fever

*Since this manuscript was submitted for publication ACTH has been administered in doses of 20 mg. intravenously in a continuous drip over an eight-hour period daily for fourteen to twenty-one days.

and hyperkalemia on the abrupt discontinuation of ACTH. No similar complications were observed when the dose of ACTH was tapered off over a period of five to six days before termination of treatment.

Other complications were moderate hirsutism, acne and pigmentation, which gradually disappeared after ACTH therapy was discontinued.

Roundness of the face was observed in all patients during the second to third week of treatment. This varied from patient to patient and diminished gradually after the treatment was completed.

The fecal lysozyme titer paralleled the clinical course of ulcerative colitis, decreasing with remissions and increasing with exacerbations. It served as a measure of the activity of the disease and the extent of the inflammatory process. Significant amounts of lysozyme are present, for example, in both granulation tissue[8] and inflammatory exudates.[9]

The consistent and often dramatic fall in the fecal lysozyme titer, observed in patients responding to ACTH therapy, probably reflects a decrease in the inflammatory process. It follows a similar pattern to the inhibitory effect of ACTH on other tissue reactions to injury and inflammation, such as fibroblast proliferation, and mobilization of tissue lymphocytes, gamma globulin, fibrinogen and complement.

The beneficial effect of ACTH may be attributed, in part, to its ability to decrease the extensive inflammatory process within the tissue and to diminish the systemic and toxic manifestations of infection. The inhibition of fibroblastic proliferation alone may prove of great value if ACTH can prevent fibrosis and stricture formation, which are among the most serious complications of these disease syndromes.

Summary

ACTH induced a definite and often dramatic remission in five of six patients with extensive ulcerative colitis in the acute phase who were incapacitated by the disease and refractory to other forms of medical management. A similarly satisfactory remission was observed in 2 patients with regional enteritis.

Relapses occurred in all but 2 patients two to nine months after the discontinuation of ACTH therapy. One patient has remained in a permanent remission for sixteen months. The patients who relapsed responded satisfactorily to a second course of ACTH or cortisone therapy. Long-term maintenance therapy and repeated courses of treatment appear to be helpful. ACTH may offer an additional supportive measure in the preparation of patients for ileostomy.

The fecal lysozyme titer, which is a good measure of the activity of the disease and the extent of the inflammatory process, fell consistently after ACTH therapy in the 5 patients with ulcerative colitis who responded to treatment.

ACTH does not constitute a cure but is a valuable adjunct in the therapy of ulcerative colitis and regional enteritis, particularly in the early stages of the disease.

We are indebted to Dr. George W. Thorn, Dr. Peter Forsham, Dr. Thomas Frawley, Dr. Thomas A. Warthin of the Veterans Administration Hospital, West Roxbury, and Dr. Rudolf Kurzmann for their interest and co-operation.

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THE SUICIDAL RISK*

Its Diagnosis and Evaluation

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IN this country about 16,000 suicides are reported each year.[1] In addition, about 100,000 suicidal attempts are believed to occur annually.[2, 3] Thus every physician may find himself in a position in which he must decide on the degree of suicidal risk that a given patient represents.

VARIETIES OF SUICIDAL RISK ENCOUNTERED IN MEDICAL PRACTICE

Suicide is a reaction common to the mentally disordered of many types. The mistaken belief that manic-depressive psychosis is the principal suicidiferous disorder may lull the physician into a false sense of security at times.

CASE 1. A man removed his mother, a patient with senile depression, from a psychiatric hospital against physicians' advice and consulted a local physician about further treatment. The doctor telephoned the hospital and was given the diagnosis by the record librarian. Without further questions he decided that this was not serious because (as he stated later) it was not a manic-depressive depression. He prescribed symptomatic medication. The woman killed herself twenty-four hours later.

Involutional melancholia slightly surpasses manic-depressive psychoses in gravity, if not in frequency of suicidal risk. Several types of schizophrenia also harbor a very dangerous suicide factor[4]; in paranoia, paranoid state, epilepsy, epileptoid syndrome,[5] general paresis (early stage mainly) and a number of psychoneuroses (notably some types of obsessive-compulsive[6] and post-traumatic neuroses) suicidal impulses may arise as part of the clinical picture.

Pathologic grief (abnormally prolonged or intense mourning characterized by irrational guilt feelings and a hypochondriacal flare-up) and reactive depression (that is, depression clearly in reaction to an adversity rather than "groundless") have been known to be complicated by suicide. Alcoholism, on the other hand, is no longer generally considered a direct cause of suicide, with the possible exception of acute alcohol hallucinosis, in the course of which terrifying hallucinations and ideas of persecution may drive the patient into a suicidal panic.

Delirium (febrile, cardiac, alcoholic) may lead to suicide in response to extreme apprehension and confused ideas of persecution, often during a semi-lucid interval.[7]

A risk that is sometimes neglected medically exists in acute panic states of various origin. Here are two typical examples:

CASE 2. A mother whose two small children had just perished in a fire in their upstairs bedroom hanged herself a few hours later. During these hours her behavior was described as "strange and bizarre, even under the circumstances."

CASE 3. A young college instructor committed suicide a few hours after having been called "queer" to his face by a favorite male student. In a scribbled note he said: ". . .the terrible truth [of his homosexuality] has suddenly dawned on me for the first time . . .I am in panic. . . anything might happen." A physician whom he had tried to talk to an hour before his death had given him a sedative and sent him home.

Suicidiferous over-reactions to despair and frustration require the physician's alertness. They constitute a substantial portion of all suicides. This group shares with the acute panic states the impairment of judgment and of the instinct of self-preservation, although in a clinically less dramatic fashion. Typical examples would be the prospect of financial, social or professional ruin under certain circumstances or a self-destructive frenzy in reaction to the feeling of being trapped (acute quandaries in blackmailing situations; narcotic addicts facing loss of supply). The tension of uncertainty or an irrational fear of what is to come may lead to suicidal over-reactions in some persons. Sexual panic has been recognized as a not infrequent and dangerous causative mechanism (such as strong homosexual desires in a repressive environment or the unheralded emergence into consciousness of incestuous desires), — also physical disfigurement or crippling in certain types of personality[8] or a patient's first learning of his malignant or incurable disease.

Suicidal acts of hysterical personalities are usually limited to "gestures" with no serious intent to die. These persons may use the threat or shock of a suicidal gesture to control their environment, to gain attention, to arouse sympathy, to frighten others into submission or to dramatize themselves.[9, 10] However, fatal accidents are apt to happen among them: leaning too far out of a window, overdosing with "harmless" drugs or miscalculating the arrival of someone to shut off the gas jets. Especially under the influence of alcohol their judgment may fail them, with lethal results.

The question of "rational" suicide (that is, suicide by a well integrated, mature person under the burden of a massive, objectively irremediable misfortune, after calm reflection) has been much debated in the medical literature. Although many authors

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‡From *suicid-* and the affix *-ferous* (bringing, making), as in *febriferous, pestiferous* and so forth. This seems preferable to both "suicidogenic" and "suicidal" as applied to a disorder (both found in the literature). The former may be misinterpreted to mean "caused by suicide"; the term "suicidal disease" permits confusion with the concept of an illness as an (unconscious) means of suicide.

consider any type of suicide a pathologic act, judgment on this point may well hinge on the definition of psychic normality that the observer adheres to and on the cultural setting and background of tradition in which the act occurs. (For example, suicide was reportedly the expected, normal step in the Imperial Japanese Army after failure to carry out an assigned task or in the old Prussian officer corps after transgression against the honor code.)

"Rational" suicides are most frequently to be expected in patients with incurable or severely painful afflictions. No systematic studies on this subject exist, but the following tentative observations are offered: In malignant or incurable illness the two most critical periods, with regard to suicide, seem to be that of uncertainty, while diagnosis and prognosis are still at issue, and that of shock following the first realization of the upheavals and suffering, true or fancied, that are to follow. Once the patient has settled into the regimen of chronic illness and its care, active suicidal thoughts tend to disappear from the picture.

As to intractably painful conditions, it usually seems to be the fear of greater future pain that arouses suicidal impulses in these patients, although unabated physical torment may conceivably lead in itself to a frenzied attempt to seek relief in suicide. Since intense suffering may mobilize latent hysterical mechanisms in some patients, the evaluation of suicidal utterances in severely ill patients is among the most delicate tasks with which the physician can be confronted in the field of suicide prognostication.

It is suggested, however, — largely as a matter of clinical expediency, — that a severely afflicted patient ruminating suicide be not allowed the benefit of the doubt of rationality (that is, the freedom of choice in disposing of his own life), and that every such syndrome constitutes a proper subject for medical preventive efforts.

Clues from the Presenting Complaint

Only a portion of potentially suicidal patients arouse medical attention with definite psychiatric symptoms. Frequently there are only vague or nonspecific complaints to alert the doctor's suspicion of latent suicidal tendencies. Table 1 affords a fair sampling of such complaints:

Ninety-four consecutive cases are presented of patients found potentially suicidal (on psychiatric consultation). All were first seen by a physician in general practice or in a general outpatient clinic.

Although some of the tabulated "general" complaints are typical symptoms of severe depression (such as insomnia, fatigue, loss of appetite and libido, inability to concentrate), it is always a diagnostic feat, especially for the nonpsychiatric physician, to detect a suicidal risk behind a vague or trivial symptom of this kind.

Clues from the Recent History

A history of a recent suicidal attempt must always be viewed with a measure of alarm. In depressive patients, for instance, it is not unusual for them to repeat the attempt one or more times if they fail.

The family may report that the patient has recently talked of suicide. Contrary to the belief that a truly suicidal person "just goes ahead and does it," many such patients do talk about their intent beforehand, — possibly as many as 40 per cent.[11] Such talk may range from melodramatic threats to matter-of-fact statements. The clinical "rule"

Table 1. *Presenting Complaints in Cases of Suicide.*

No. of Cases	Complaint
12	Directly suicidal symptoms (recent attempt, talk about suicide, suicidal preoccupations)
21	General psychiatric symptoms ("nervous," "depressed," "memory slipping," "can't concentrate," "foolish thoughts and daydreams," panic reactions, abnormal grieving)
11	General physical symptoms (fatigue, "don't feel right," "always tired," "heavy feeling," numbness)
10	Digestive and nutritional symptoms (mostly loss of appetite and weight, "indigestion")
9	Insomnia or request for sleeping tablets
5	Continuous self-dosing with sedatives during daytime (3), drug addiction (2)
4	Dysmenorrhea, amenorrhea, "menopausal troubles"
4	Loss of sexual desire, impotence (In all 3 impotent patients this was a symptom, not a cause of a suicidiferous depression.)
3	Episodic alcoholism
5	Under care for a chronic disorder (neurologic, malignant disease)
1	Obstinate eczema with secondary infection (scratching due to agitated depression)
1	"Frequent colds" (patient kept to his bed excessively with dubious colds, actually because of depressive apathy)
1	Desired rhinoplasty (manic-depressive, mixed type)
1	Desired circumcision (no genitourinary disease found; impulsive schizophrenic)
6	Suicidal tendencies an incidental finding (1 cardiopathy, 1 infectious mononucleosis, 1 tonsillitis, 2 prenatal examinations, 1 frequent colds)

that the suicide risk decreases with the increasing emotionality of the self-destructive utterances has too many exceptions to be trustworthy.

The finding of a hidden or discarded farewell or other suicide letter should serve as a warning symptom. Some severely suicidal patients expend great pains on the composition of their notes, often making several drafts. It may, of course, represent a hysterical device (to arouse sympathy or to frighten) and the note may be left where it is certain to be discovered, but if the subject is an adult in a state of depression, such notes must be regarded with pessimism regardless of how convincingly the patient tries to explain them away.

Patients who appear to have recovered recently from a serious depression must be regarded with special caution. Suicide not infrequently occurs at precisely that stage.

A patient reported to be making plans for the future while in a state of depression (buying new clothes, theatre tickets, a house, or making dates, appointments, travel reservations or other commitments) may still be suicidal.

CASE 4. A man of 37, an executive, was suffering from a depression. His wife, alarmed over his insomnia and brooding, asked the family physician to call. The doctor visited and suspected a depressive psychosis but became reassured about the possibility of suicide when the wife showed him a carefully made four weeks' schedule of inspection trips to outlying branch offices that she had found in the patient's pocket. A week later the patient killed himself.

Sometimes such future arrangements by a suicidal patient serve the purpose of allaying the suspicion of his family until such time when he is "ready" to die. Such cunning is found even in the severest type of psychotic depression. Other patients, deeply preoccupied with thoughts of suicide, continue to live "automatically," and their daily routine may well include the making of future commitments.

CASE 5. A housewife ordered from her grocer the weekly family rations, including a week's supply of her own special diet food, the morning of the day on which she attempted suicide. She explained later that she had given "no special thought" to the nature of her purchases. She had been contemplating suicide for weeks.

In deeply depressed patients there may be a history of physical and mental activity's having recently become an effort, inability to work efficiently, inability to make decisions, loss of interest in social and hobby activities, neglect of personal appearance and cleanliness and general loss of "zest for living." There may be restlessness to the point of pacing the floor incessantly or inability to sit through meals. The patient can barely make himself get up in the morning and face the new day, although he may pick up somewhat during the late afternoon and evening (a minor and inconstant differential-diagnostic point; patients with neurotic-type, that is, usually nonsuicidiferous, depressions tend to be more listless and downcast toward evening).

As to general health in cases of suspected suicidiferous depression there is often fatigue, loss of appetite and weight and constipation. Sexual desire diminishes; in men potency may be impaired, in women there may be dysmenorrhea or amenorrhea. Insomnia is often marked, and sleep is no longer refreshing.

Grounds for depression are among the most difficult factors to evaluate. The empirical tenet that only "groundless" depressions are truly suicidiferous has been somewhat discredited as more and more varieties of suicide have come under psychiatric scrutiny. Occasions such as loss of employment, financial reverses, disappointment in love, grief over an erring child, or threatened exposure of a misdeed have all been known to lead to suicidal impulses in certain persons. More frequently, however, the purported reason for the suicidal attempt is purely delusional.

CASE 6. A 47-year-old man told his family that he was about to lose his job. He had overheard "unmistakable remarks" about his inefficiency, and had "read the truth" in the face of his superior. He was very depressed (which everyone found justified), and his friends and family commiserated with him, especially as he convincingly described the difficulties of finding a new job for an "inefficient man of my age." Unexpectedly he committed suicide shortly thereafter. Inquiry revealed that no one had ever thought of discharging him. His beliefs had simply been early delusional-type symptoms of a suicidiferous depression.

A history of recent, unprecedented and apparently unmotivated overindulgence in alcohol, often with prolonged "hangover blues," should arouse some suspicion. Deeply depressed patients sometimes resort to drink in an attempt to relieve the discomfort associated with the unrecognized depression — especially their unaccustomed difficulties in talking with people, their fatigue, restlessness, apprehensiveness and so forth. In some such persons alcohol may facilitate the emergence of underlying suicidal drives. This syndrome occurs also in some dipsomaniacs (periodic drinkers) who are actually suffering unrecognized manic-depressive episodes. Likewise, some unrecognized schizophrenic and paranoid patients may resort to drink in order to "drown" the hallucinatory "voices" that urge them to kill themselves or in order to escape relentless ideas of persecution. Under the influence of alcohol they may become even more terrified and kill themselves in sudden panic.

CLUES FROM THE PATIENT'S PAST HISTORY

In the presence of a depression, search must be made for one or more previous episodes of depression of limited duration (usually two to eight months if untreated), in order to rule out a manic-depressive psychosis. For the same reason previous manic and "mixed-type" episodes must be searched for. The absence of suicidal attempts during previous depressive attacks is no guarantee against self-destructive impulses during subsequent attacks, although the risk is generally less serious in these cases.

An evaluation of the patient's pre-illness personality is rarely worth while in terms of present suicidal risk, especially for the nonpsychiatric physician. Suicidiferous disorders have occurred in every imaginable type of personality and character structure, and no reliable method of correlating past personality and suicidal risk exists to date.

An important observation, first made by Zilboorg[6, 12] is that a serious suicidal risk exists in certain despondent persons whose father, mother, guardian or other "important" relative died when the patient was between the ages of four and six or between ten and thirteen.* There are valid-appearing theoretical reasons for these particular ages. Clinical experience seems to be confirming this finding, and a conscientious history should include a search for it.

A *family history* of mental or emotional disorders, alcoholism, epilepsy, criminal tendencies and so forth is without specific significance in terms of suicidal risk.

*Limited to cases in which the dead relative was the object of patient's ambivalence, for example conflicting but coexisting feelings of love and hate. Since the diagnosis of ambivalence requires specialized psychiatric skill, the physician is best served if he simply establishes the fact of an early death and regards a positive finding as a corroborating sign only.

However, a family history of suicides among the immediate ascendants may have minor corroborative importance. Although the tendency to suicide itself is certainly not hereditary, findings such as the following have been made: Among 61 cases of suicidal attempts there were 32 cases of suicide by immediate ascendants[12]; in another series 6 out of 22 children and adolescents who had attempted the act had a positive suicide history in the immediate family.[14]

Evaluation of Previous Suicidal Attempts

Such an evaluation can be helpful in differentiating a hysterical type of suicidal gesture ("trivial attempt") from a "serious" one that happened to fail. This is frequently of prognostic importance.

The seriousness of previous attempts is often misrepresented to the physician. A suicidal patient may minimize his previous attempts in order to reassure the doctor and forestall preventive measures. Other patients may have actual amnesia for the past circumstances and supply fictitious details for the story. Or a member of the family, in giving the history, may unwittingly "inject" his lingering shock or chagrin into it, thus overdramatizing it, or he may minimize it out of shame, embarrassment or even wishful thinking. Thus it is up to the attending physician to establish as many objective circumstances as possible for his evaluation. The following factors may have significance:

The means employed in the attempt may be an indication of its seriousness. Patently dangerous means (leaps from high places, shooting in head or heart region, throwing self in front of rapid train or truck) rule out triviality, as do most cases of hanging and drowning. The evaluation may be more difficult in instances of cutting, gassing, poison and overdoses of hypnotics. Ineffectual means such as superficial cuts, sublethal doses of hypnotics or dosing with iodine, cough medicine or other bathroom-cabinet contents usually indicate a trivial attempt, although exceptions have been noted. In the latter category the possibility of accidental overdosing or misdosing (as in a toxic confused state) must be kept in mind, although some observers feel that in most such "accidents" an underlying (subconscious or unconscious) suicidal impulse can be found. Cruel or bizarre means (pounding head against cement wall, slitting throat ear to ear, lying down in front of steamroller, igniting self, thrusting red hot poker down the throat)[9, 15] are usually evidence of dangerous psychopathology and are hardly ever "hysterical." The swallowing of foreign bodies (glass, nails and so forth), even though it may be ineffectual, usually takes place in serious psychoses only and thus cannot be called trivial. Multiple means (poison with hanging, sleeping tablets with drowning and so forth) are always evidence of serious intent.

The presence or nearness of other persons is not necessarily evidence that the attempt is a hysterical gesture. Suicide of almost any type has been committed with other persons in the same room — either directly after quarrels, threats, dares or exalted scenes or without any warning. In fact, a considerable proportion of patients who have made "exhibition-type" attempts (perching on ledge, tree or rail before an audience) have been found to harbor deep-seated suicidal drives in conjunction with a psychosis. With these exceptions in mind, however, triviality can be surmised in the majority of attempts that were "arranged" to be promptly discovered or prevented, even after consciousness had been lost. Depending on the patient's sophistication, such gestures may be either crudely transparent or cleverly contrived. Moderate cleverness would be exemplified by the following case:

Case 7. A young woman who was caring for her rather despotic invalid mother drank the contents of a bottle of chloral hydrate belonging to the mother. She did this at about 6:30 p.m. Her mother had long been in the habit of taking a spoonful from this bottle precisely at 7 p.m. every day. The attempt was promptly discovered and the girl survived.

Suicidal attempts that include the (attempted) killing of others cannot be counted as trivial for purposes of risk prognostication.

Case 8. A man living with his wife in a small apartment turned on the gas one night while his wife was asleep. The odor was discovered shortly by a neighbor, and the janitor entered the apartment in time. To the police the man maintained that he had merely wanted to "frighten" his wife because of her nagging. He was believed, even by his wife, and no psychiatric examination took place. Two weeks later the man killed himself.

Both extreme impulsiveness of an attempt (such as leaping through an unopened window) and minute preparation (such as hotel registration under an assumed name in another town, removing identification from pockets and clothing, rigging mechanical suicide contraptions) usually bespeak the patient's seriousness of intent, although there are exceptions.

The patient's reaction after the thwarting of an attempt may have prognostic importance. An obvious feeling of relief and expressed gratitude for having been rescued usually make the danger of repetition slight. The same is true if the dramatic episode he has just gone through seems to have completely relieved the patient's morbid mental state (such as depression) prevailing before the attempt. On the other hand, if the patient appears sullen, downcast or even enraged[13] after having been rescued or revived, he usually presents a poor risk.

Clues from Patient's Behavior and Appearance

Among major mental syndromes all cases of agitated depression must be considered potential suicide risks. The grossly agitated patient moves about almost continuously, tears his hair, picks his skin, may strike himself and barely responds when spoken to. His facial expression conveys despair and apprehension. In less extreme cases the patient

shows signs of restlessness, rubs or picks at his skin, wrings his hands surreptitiously and sways or rocks slightly when sitting. His speech, demeanor and expression convey despondency.

Slightly less suicidiferous are cases of depressive stupor, but they require close surveillance. Here the patient is almost immobile, does not talk and may not take nourishment or attend to his bodily functions. His features may convey despondency. The differential diagnosis (from catatonia, for instance) is often difficult but is important.

In other obviously "disturbed" mental patients, a preponderance of impulsive-assaultive behavior indicates the presence of a suicidal risk of varying degree. A detailed evaluation of the risk factor in such cases may not be necessary, since the need for psychiatric hospitalization is usually clear in these cases.

Special attention must be paid to the presence, in otherwise quiet persons, of auditory hallucinations. The patient listens intently to "voices" he alone hears or even converses or quarrels with them. Some authors believe that such voices, urging, taunting or ordering the patient into self-destruction, are a frequent cause of "unexplained" suicides.

In acute panic states leading to a suicidal attempt the patient's symptoms may vary from a "frozen," glassy-eyed daze to verbose, fidgety agitation. A noteworthy diagnostic feature seems to be the absence of suffering in the facial expression of these patients.

Despondency is among the most difficult symptoms to evaluate in terms of suicide risk. It occurs in a vast array of depressive states, ranging in gravity of risk from the lachrymose, unhappy adolescent to the moderately agitated self-accusatory dejection of the involutional melancholic. The most frequently encountered clinical picture of a case of suicidiferous depression is the following: The patient's facial expression is perplexed, troubled or even immobile. He tends to stooped posture, and his movements and responses are decelerated (psychomotor retardation). He speaks hesitantly, with difficulty, and sometimes in a very low tone of voice. Conversation, especially small talk, may be painfully difficult. Generally he seems sad, unhappy, withdrawn, without much hope and of little "warmth" or he may be irritable and distrustful. If he exhibits despair, it tends to be quiet rather than melodramatic, although some suicidal depressed patients are very "theatrical" in the expression of their suffering.[16]

Diffuse weepiness is not generally considered a characteristic sign of suicidal depressions, although exceptions have been noted. Dry-eyed sobbing accompanying overt despondency in an adult should be viewed with some alarm, as should be moaning and groaning not referable to physical distress.

Neglected appearance and persistent untidiness in a depressed patient who is normally neat and tidy should arouse suspicion. Though not in itself a sign of suicidal tendencies, it often indicates a serious degree or type of depression (the patient has ceased to care).

Evaluating the Patient's Thoughts

Most normal persons have thoughts of suicide at one time or another, without prolonging them into suicidal brooding or translating them into actual impulses and attempts.

Fifty apparently healthy, normal persons (27 men, 23 women; physicians, nurses, clerical workers, cleaning and kitchen workers, businessmen, housewives and college and medical students), chosen at random, were questioned informally about suicidal thoughts and impulses. Seven could not, on earnest reflection, remember ever having thought of it. To 4 the thought seemed abhorrent, and they denied it quickly or even became angry and refused to discuss it or think about it. The remaining 39 admitted such thoughts, ranging from "once or twice" to "every once in a while." (Note: No statistical validity is claimed for this small survey. It was conducted for purposes of orientation only.)

Knowledge of this fact is important, as the physician at times has to reassure a patient that the mere presence of transitory suicidal thoughts is not in itself abnormal.

The most frequently encountered morbid thoughts pointing to possible suicidal tendencies are baseless self-accusations ("I have done something wrong") and self-deprecation ("I am no good") in depressed patients. These thoughts may range from the quasi-realistic to the absurd. A successful, hitherto contented person may suddenly call (and consider) himself a lifelong failure, unworthy of his position or other good fortune. He may call himself lazy, incompetent, cowardly, a disgrace to his community, a burden to his family. He may accuse himself of being a sham and a fraud, sinful, deceitful, negligent of his obligations. He may believe himself the greatest criminal of all times or the cause of illness in his family, of the slums in his city or of all the poverty and bloodshed in the world.

In the words of Bond,[17] he is a person whose conscience has gone "haywire." His suffering is real and intense. If he believes that his "crimes" are great, he must pay for them with his life (suicide), although sometimes his death wishes take the milder form of longing for "sweet death" and "eternal release" (from his own conscience, as it were).

Hypochondriacal thoughts in a depressed patient need careful evaluation. The true, neurotic-type hypochondriac is actively worried about his symptoms; he may tell his physician how he proposes to "end it all" if he does not obtain relief but in the same breath begs the physician to examine his heart once more. The depressed pseudohypochondriac cares much less about his numerous symptoms ("It does not matter if I die from it"). His com-

plaints tend to assume an almost delusional character at times (such as "my intestines have dried up").

Some discernment is required if a patient harbors a fear that he might commit suicide. In most cases this represents a typical (neurotic) phobia, quite harmless as to suicidal risk.

Case 9. A young student complained of insomnia, palpitations and fear that he would kill himself. The latter sometimes amounted to near-panic. He did not go near open windows or subway stations. One he became so upset on a high bridge that he begged friends to call an ambulance. He was admitted to a psychiatric ward for ten days. Similar incidents happened repeatedly over a period of years, but he never made an actual attempt.

These are the patients who are terrified, by accounts of suicides, that they may go and do likewise. On the other hand, if such fears occur in the course of an obvious and persistent depression, caution is indicated; a despondent patient who insistently asks that a certain knife or scissors or other dangerous object be removed from his presence or that his room be moved to the ground floor should be heeded.

Feelings of spite, revenge and self-pity elicited in connection with suicidal preoccupations or threats are not so harmless as is often believed. Patients have killed themselves as "revenge" against a recently deceased relative (for leaving the survivor behind helpless)[18]; others have actually thrown their lives away to make a spiteful gesture "perfect." In some persons of this type the capacity for dealing with reality is so poorly developed that they behave as if they could kill themselves without dying.

Ideas of persecution, if persistent and distressing, may lead to suicide in a state of acute terror or even as a supreme gesture of impotent rage against the unseen "tormentors."

Clues from Direct Questioning About Suicide

It is suggested that it would be sound practice in every case in which suicidal tendencies are suspected to ask the patient if he intends to commit suicide. The danger of "putting ideas in the patient's mind" appears negligible (no bona-fide case of mobilization or precipitation of suicidal impulses caused by a properly put question of this type has been described in the literature or come to the author's attention), certainly so if reckoned against the benefits of a frank approach in terms of diagnosis, risk prognostication and sometimes even therapeutic effects (such as psychic "catharsis"). Well known exceptions are suggestible patients suffering from anxiety hysteria in conjunction with a mild depression, who sometimes come to believe that the physician's question about suicide implies a belief on his part that they may soon become suicidal. However, these patients hardly ever represent a serious suicidal risk under any circumstances.

Some patients, — or more often a relative, — may react with resentment to this question, but with an understanding and calm approach the physician can usually cope with these outbursts. It is suggested that in difficult differential-diagnostic situations the question can be asked regardless of the patient's age, intelligence, degree of sophistication, religious beliefs or sensitivity.

For optimal results the patient should be asked this question when no relatives or friends are present. With some patients this is understandably a tense moment. In these cases it is better to ask casually, while taking the blood pressure, for instance, or during some other clinical procedure. The doctor's tone of voice should be friendly, but matter-of-fact. Especially avoided should be "minimizing" ("Just a routine question. . .") and negative prompting ("You aren't thinking anything like that, of course, but just let me ask you. . .").

The wording of the question can be adapted to the patient's sensibilities. The following are examples of phrases that have been found "acceptable" to a variety of patients:

Well now, everybody who feels that way has a few suicide thoughts; can you tell me about yours?[19]

Are you thinking of doing away with yourself?

Have you been worried about suicide?

Do you feel you may do something rash (foolish) (to yourself)?

Do you feel you would be better off dead?

I am a little worried that you will. . . .

I suppose you are so miserable that you want to. . . .

Are you being driven to kill yourself? (To patients with ideas of persecution)

Are "they" telling you to die? (In dealing with patients who hear voices)

The patient's answers cannot usually be accepted at face value, of course, but certain responses may be considered significant.

The most frequently reassuring reply that can be obtained is a qualified denial of some sort ("I wish I were dead, but I wouldn't lay hands on myself." "I am thinking of it, but . . . too much of a coward . . . won't do that to my family . . . my religion prohibits . . ."). A plain "No," or unadorned denial, for instance in an obviously depressed patient, has little diagnostic value and should be discounted.

A hedging reply ("I don't know what to say," "Who can say?," "How much can a person take?") has nothing reassuring about it and is almost as significant as a veiled admission ("There seems to be no other way").

Unadorned admissions, brashly or defiantly uttered, have no clear prognostic value unless carefully explored. They are observed in some schizophrenics (dangerous), in an occasional mixed type of manic-depressive (dangerous), in hysterical psychopaths (usually harmless) and in adolescent maladjustment (harmless if handled properly).

If the question releases a flood of self-accusations ("I am unfit to live") or of hopelessness ("What's the

use of going on?"), it should be counted as a veiled admission of intent. Similar significance often obtains if the patient instead of answering clasps his head in his hands and moans or groans.

On the other hand, a sudden outburst of tears and sobbing in response may be interpreted as a favorable sign.

Outbursts of anger and indignation in response ("How dare you ask?," "This is silly," "I'm not crazy") are not always to be taken in a reassuring sense. Mixed-type manic-depressives, especially if of irritable disposition, have been observed to react this way shortly before they attempted suicide. The same holds true for occasional paranoid patients with suicidal tendencies.

If a patient replies that he has had suicidal preoccupations recently but "not now," the physician cannot be fully reassured. With the exception of certain fulminating or overwhelmingly impulsive syndromes the suicidal patient's struggle with his instinct of self-preservation occupies a lengthy period of time. The patient's suicide thoughts come and go, periods of strong death wishes alternating with days or weeks of relative calm. Over-optimism based on ignorance of this fact may have tragic consequences.

Clues from the Physical Examination

There are no specific findings in suicidal patients, but a few may have corroborating value.

One or more transverse scars on the flexor surface of the wrist are positive proof of a previous attempt. Probably no other injury produces this type of scar, regardless of what the patient may say. Two cases have been seen in which feebleminded women had attempted to cut their wrists lengthwise. Linear scars about the neck should also be investigated.

In depressions the following syndrome is seen almost exclusively in the psychotic (more suicidiferous) type of patient: a combination of weight loss, some dehydration, cold and cyanotic extremities, slightly shallow respiration and sometimes a labile pulse rate. The basal metabolism may be depressed.

In cases of agitated depression patches of hair may have been torn from the scalp, and the skin may show evidence of constant rubbing and picking.

Conclusions

In every patient with suspected suicidal tendencies a careful evaluation of the risk is necessary in order to apply preventive measures and bring the patient to treatment. In many cases it seems more important to evaluate individual behavior manifestations and other symptomatic evidence, both objective and subjective, rather than to insist on a diagnosis of the underlying disorder. Because of our as yet limited knowledge of psychic processes this empirical approach often protects the physician from being lulled into a false sense of security.

Clinical tests to establish the presence or seriousness of suicidal thoughts do not exist. Attempts have been made to use existing psychologic tests[20,21] for this purpose, but their usefulness appears limited. The uses of lie detectors (Keeler polygraph) and psychogalvanic devices have not been explored.

Few suicides occur without preceding early manifestations or symptoms of mental upheaval. These early symptoms may have been present for months, and the conscientious physician will guard against an attitude of "letting sleeping dogs lie." Prompt recognition of a latent suicidal risk may actually save the patient's life.

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AUREOMYCIN IN THE TREATMENT OF INFECTIOUS MONONUCLEOSIS

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CONFLICTING reports on the effectiveness of aureomycin in the treatment of infectious mononucleosis have appeared in the past year. Lyons and Hard[1] studied 43 cases, — 25 controls and 18 treated patients. They shortened the average days of hospitalization from thirty-nine days to twenty-six days and the average length of the disease from forty-four days to thirty-two days; the duration of fever and liver involvement were strikingly less. Symptoms cleared in forty-eight hours. Other workers have had less favorable results. Seifert and his co-workers[2] treated 47 patients by giving aureomycin or a placebo to patients at home and estimating results on subsequent visits. In 34 trials in proved cases, 4 of 13 (30 per cent) were "cured" by placebos and 9 of 21 (43 per cent) were "cured" by aureomycin. The difference is not significant. Others[3, 4] have shown a poor response in a small number of cases. We have tried to evaluate the use of the drug in 16 cases of infectious mononucleosis in college students.

METHODS

All patients with a preliminary diagnosis of infectious mononucleosis were seen by one or both of the authors. In addition to a complete clinical examination on admission, the following studies were done routinely: throat culture, white-cell count and differential count (every three days) and a sheep-cell agglutination (every week). Attention was paid to the size of the spleen and lymph nodes and the duration of their enlargement or tenderness. Alternate patients received either aureomycin or a placebo with the same appearance. Milk was used to control nausea caused by the drug. No aluminum hydroxide in any form was given. The treated patients received 1.0 gm. of aureomycin initially and 0.75 gm. every six hours thereafter in most cases. The average total dose was 15.75 gm.

Because of our desire to begin treatment as early as possible, aureomycin therapy frequently was initiated before the diagnosis of infectious mononucleosis could be confirmed. The average hospital stay prior to aureomycin therapy was 1.5 days. Any case that did not meet the criteria of a sheep-cell agglutination titer of 1:224 or greater and a diagnostic blood smear was discarded from the series. This resulted in the omission of several patients from both the treated and the control group. For purposes of comparison, the last 2 untreated cases just prior to the initiation of the study were included, making a total of 16, — 8 treated patients and 8 controls.

TABLE 1. *Laboratory Data on 16 Patients with Infectious Mononucleosis.*

CASE	NO. OF DAYS OF ILLNESS PRIOR TO ADMISSION	NO. OF DAYS IN HOSPITAL PRIOR TO TREATMENT	TOTAL DOSE	NO. OF DAYS IN HOSPITAL	NO. OF DAYS OF FEVER IN HOSPITAL	NO. OF DAYS OF FEVER FROM ONSET OF ILLNESS TO DEFERVESCENCE	MAXIMUM FEVER	HIGHEST WHITE-CELL COUNT	HIGHEST PERCENTAGE OF LYMPHOCYTES	HIGHEST HETEROPHIL COUNT
			gm.				°F.	$x10^3$		
Control:										
1	7	—	—	12	10	17	103.2	13.0	59	1/224
2	7	—	—	17	14	21	102.6	14.0	76	1/3584
3	7	—	—	8	3	10	102.8	7.0	44	1/224
4	2	—	—	27	23	25	102.6	13.0	85	1/3584
5	10	—	—	19	6	16	103.6	17.0	75	1/224
6	14	—	—	30	26	40	100.6	14.0	88	1/448
7	14	—	—	8	4	18	99.4	8.0	67	1/224
8	14	—	—	10	7	21	100.2	13.0	68	1/448
Averages	9.4			16.5	11.5	21	101.9	12.5	70	—
Treated:										
1	(30?)*	3	18	17	13	?	102.0	28	87	1/3584
2	14	1	12.5	15	10	24	102.4	9	78	1/224
3	10	1	20.25	33	12	22	103.0	29	90	1/3584
4	7	2	21.0	19	17	24	104.0	24	79	1/3584
5	14	2	21.0	10	2	16	99.0	8	34	1/224
6	14	1	12.5	12	7	21	104.0	22	94	1/3584
7	1	1	8.5	5	3	4	99.0	9	87	1/224
8	2	2	12.5	12	9	11	102.8	8	79	1/224
Averages	9	1.5	15.5	15.5	9	17.4+	102.2	17	79	—

*This figure was not used in calculating the average number of days prior to admission to the hospital or in calculating the number of days of fever from the onset of illness to defervescence.

RESULTS

Table 1 illustrates the course of each patient. The cases in the two groups were of approximately

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equal severity, as shown by the data presented. The exact duration of symptoms could not be determined accurately, as a rather long convalescence continued after discharge from the hospital. We used the duration of fever as the most objective measure of the effect of the drug on the course of the disease. This figure we calculated from the onset of symptoms before admission to the defervescence of fever in the hospital. We did not use the number of days of fever in the hospital alone, as patients were admitted at widely varying times after the onset of their symptoms. The difference of three and one-half days in the duration of fever between the two groups was not significant. Moreover, no correlation was observed between the number of days of symptoms prior to treatment and the total duration of the treatment. In other words, hospital care alone did not alter the duration of the illness. Four members of the control group (Cases 3, 4, 5, 6) and 3 of the treated patients (Cases 2, 3, 6) developed a moderately severe stomatitis and pharyngitis during the period of observation. These patients, generally, were the sickest, but, as can be seen from the data, aureomycin did not shorten the duration of their fever. In both groups, fever fell by lysis over four or more days and no dramatic subjective changes occurred. The symptoms of pharyngitis, malaise and headache, as well as the signs of adenopathy, pharyngitis and splenomegaly, seemed to persist for approximately the same length of time in both groups. No significant change was noted in the white-cell response or in the sheep-cell agglutination. A slow convalescence was the rule for some time after discharge from the hospital.

Summary

Sixteen cases of infectious mononucleosis have been observed by us during the last year. Eight patients were treated with aureomycin and 8 served as controls. No significant change was noted in the clinical course of the patients receiving aureomycin.

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MEDICAL PROGRESS

BCG VACCINATION

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MANY excellent articles and reviews[1, 2] on the different phases of BCG vaccination have appeared in the literature. Since a compilation of the results of these articles was thought to be of interest, the present review was prepared.

In 1906 Calmette and Guérin began their experiments in an attempt to find a viable attenuated strain of bovine tubercle bacillus. In 1920, after 250 generations of growth, they finally found a strain that would produce only a localized lesion when injected into an animal. The first attempt at human vaccination with this vaccine was accomplished by Weil-Halle in 1921. Petroff and his associates[3] alarmed the medical world in 1931 when they reported that they had produced a return of virulence in the organism by routine laboratory methods, but they later conceded that BCG was probably a pure form that was incapable of producing progressive disease.

BCG is a suspension of living bovine tubercle bacilli obtained from cultures of a strain so attenuated as to be incapable of producing progressive disease when injected into experimental animals. The lesion produced remains localized. The vaccine is cultured on specific media such as bile potato, Sauton's medium,[4] glycerin broth or glycerin potato.

In accordance with the minimum requirements published by the National Institute of Health in 1949,[4] potency can be determined by either animal or human assay. In animal assays, a guinea pig weighing 400 gm., is inoculated, by multiple punctures, with a 15- to 20-mg. per ml. dilution of BCG vaccine. On the intradermal injection of a heavy dose of Old Tuberculin (10 mg.) one to three weeks later, there should be seen an area of induration 10 mm. or larger after forty-eight to seventy-two hours. During this time the pig gains weight.

In human assays, the vaccine should show the tuberculin conversion record in not less than 10 consecutive tuberculin-negative persons (preferably

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under twenty years of age) when tests are made six to eight weeks after the inoculation. At this time, at least 80 per cent of those tested should yield a positive reaction. A subject is considered acceptable for inclusion in the test if he gives a negative reaction to the intradermal injection of 0.1 mg. of National Institute of Health Old Tuberculin reference standard, or the equivalent of 0.0002 mg. of purified protein derivative reference standard. Newborns may be used without previous tuberculin testing.

The bacterial count of the vaccine as harvested, 1 mg. of moist weight growth from which the finished vaccine is subsequently made, should show not less than 20,000,000 colonies when plated in the proper dilutions on a suitable solid medium or visible growth in the proper dilutions when cultured in a suitable liquid medium. From presently available data, it is not possible to specify the required number of viable organisms required to be injected in the intended immunizing dose, as either a liquid or a dried vaccine. There is some evidence that the number of nonviable organisms present may play a significant role. However, according to Dubos,[5] the vaccine contains 1,000,000,000 to 5,000,000,000 bacteria per cc. of fluid, and only a fraction of 1 per cent of these are viable at the time of injection. Consequently, the practice of giving directions in terms of cc. or mg. of vaccine is misleading and meaningless. Aside from the viability of the bacteria, the physiologic state must be considered, for in its preparation the vaccine is exposed to a number of physical and chemical traumas; thus each vaccine consists of an unpredictable mixture of cells possessing all degrees of physiologic age and activity. Dubos[5] further states that at this time no well defined technic for assay exists and that the comparative dose for animals is too large for human beings.

The sterility of the vaccine is assured by the absence of extraneous growth when it is cultured on thioglycolate media for seven days. However, a liquid vaccine may be released after twenty-four hours' incubation if no growth has developed, but it will be immediately recalled if any growth does develop in the following six days. Smears and cultures of the vaccine are then made that must be typical to assure the identity of this strain.

The avirulence of the vaccine is assured by testing the seed culture and each lot of vaccine by injecting it subcutaneously, intramuscularly or intraperitoneally into guinea pigs. At least 2 out of 3 guinea pigs during a six months' period after inoculation should show no evidence of progressive disease on clinical and post-mortem examination. In addition, these pigs should show a positive tuberculin reaction, in four to six weeks after inoculation, to a dose of 1.0 mg. of Old Tuberculin or 0.005 mg. of PPD. One cannot forget the Lubeck disaster of 1929, in which 77 of 271 orally vaccinated children died because virulent organisms were used, as a result of faulty laboratory technic. There have been other little-publicized disasters in Hungary and Chile of a similar nature.

The vaccine has a life of five to fourteen days, but even this is conjectural. Most authorities agree that the usable life expectancy of the unstable vaccine is five days.

At the present time, the criterion for a successful vaccination is the conversion of a negative tuberculin skin test to positive. It appears from the average of reports in the literature that an allergic response to the Mantoux test will be produced in about 80 per cent of persons who are vaccinated with BCG. Anderson and Palmer[6] state that the hypersensitivity produced by BCG varies, and to report more than 90 per cent conversion rate of the Mantoux test one must be most liberal in the interpretation of the reaction to even the strongest tuberculin dose. A six- to eight-week post-vaccination period is necessary for conversion of the Mantoux reaction from negative to positive.

The theory of BCG vaccination is that exposure to the tubercle bacillus and the development of a positive tuberculin test will produce a certain degree of immunity to tuberculosis. Dubos[5] has stated that unfortunately the relation of allergy to immunity in tuberculosis is still obscure. The injection into cattle of dead tubercle bacilli as well as BCG under certain conditions can produce allergy to the tubercle bacillus without immunity. Another consideration is that persons who are probably the least likely to develop a good immunity are often those who are living under the poorest environmental conditions.

Anderson and Palmer[6] have shown in preliminary reports that the percentage of children who were Mantoux positive six months after vaccination was decreased by 75 per cent three years later. Jacox and Meade,[7] using two different strains of BCG, found that one strain produced only 10 per cent positive tuberculin tests one year after vaccination, in contrast to the other strain, which caused the positive tuberculin reaction to persist longer than one year in all vaccinated cases. Others have reported a persistence of the positive Mantoux test in 88 per cent of subjects for as long as five years, but these persons were tested with a stronger tuberculin dosage. Many authorities believe that the immunity persists for at least five years or more but not so long as that gained from naturally acquired contact. It has been stressed that BCG vaccination is not preventive to the degree that the smallpox vaccination is, and that persons who have had successful vaccinations have died later of pulmonary tuberculosis of the reinfection type.

Anderson[8] reported that "on July 12, 1950, the U. S. Public Health Service licensed the Research Foundation and the University of Illinois for 'man-

ufacture, exportation, importation and sale' of BCG. The intent thereof was that the vaccine produced by the licensed laboratory should be safe by trial with animals, free from contaminating substances and produce a satisfactory immediate reaction in animals and human beings when used within the prescribed time limit." The vaccine, therefore, was permitted to enter interstate commerce and be available to health officers and clinicians who wish to use it as a protective measure against tuberculosis. However, he warned against the indiscriminate and wholesale use of it, believing that all requests for BCG should be carefully reviewed.

Since BCG is still in the evaluation stage, the groups that are recommended for vaccination are[6, 9, 10]: doctors, nurses and medical students who are exposed to infectious tuberculosis; all hospital personnel and laboratory personnel whose work exposes them to contact with tuberculosis; persons who are unavoidably exposed in the home to infectious tuberculosis; patients and employees of mental, penal and other institutions in which the incidence of tuberculosis is known to be high; and children and adults who are considered to have inferior resistance and who live in communities in which the tuberculosis rate is high.

The American College of Chest Physicians[11] recommends that only the investigation of vaccination in tuberculosis be continued, and they do not advocate the groups listed above for vaccination. They state further that such fundamental matters as the preparation of the vaccine, the method of vaccination, what constitutes a successful vaccination, how resulting immunity may be measured and how long immunity persists should be determined before widespread use is advocated.

The contraindications for BCG vaccination are the following: positive tuberculin reaction — some investigators exclude those who react only to the first-strength tuberculin, whereas others exclude those who react only to the second-strength tuberculin; acute infectious diseases (until these have subsided); diseases of the skin; and active tuberculosis.

Experience with tuberculin skin testing is a prerequisite for those clinicians who are engaged in BCG vaccination. The degree of erythema is not considered in reading the reaction, but an area of induration 6 mm. or more in diameter is usually considered a positive reaction in forty-eight to seventy-two hours after injection.

There has been disagreement concerning whether PPD will produce as many reactors after vaccination as will Old Tuberculin. In trials by the U. S. Public Health Service in penal institutions, Anderson and Palmer[8] reported that PPD in the intermediate dose of 0.0002 mg. was even slightly better in producing positive reactions than 0.1 mg. of Old Tuberculin.

The procedure for vaccination that is recommended by the licensed producer[10] is as follows:

Written consent of the patient or parent-guardian

The Mantoux Test

Newborns are not tested.

Persons with no known tuberculous contact are first skin-tested with PPD 0.0002 mg. or 0.1 ml. of 1:1000 Old Tuberculin.

If these tests are negative, the subjects are then retested with the next stronger dilution until the top dose of PPD 0.002 mg. or 0.1 ml. of 1:100 Old Tuberculin is reached.

It is preferable for all subjects to have a chest x-ray examination. The reactors must have this examination to rule out any active disease, as well as the nonreactors.

All nonreactors are vaccinated with BCG. The vaccination should be given immediately after the last Mantoux test, — never more than two weeks after the test.

Six to eight weeks after vaccination the vaccinated subjects are retested for a tuberculin reaction.

The remaining nonreactors are then revaccinated.

Once a year the vaccinated subjects, as well as the controls, are retested for the tuberculin reaction and a chest x-ray film is taken.

Anderson and Palmer[8] state that a few years ago the persons who reacted only to the stronger tuberculin dose were excluded from vaccination, whereas today the criteria for such has changed and more persons are now considered eligible for vaccination; therefore, some who may react only to the strongest tuberculin dose are vaccinated.

The technics of vaccination are varied.[6, 10, 12, 13] The customary site is the outer aspect of the left arm or thigh. The site is prepared by rubbing the skin with acetone or 70 per cent alcohol.

Transcutaneous Multiple-Puncture Method

Rosenthal disk. A thin, wafer-like stainless-steel plate, from which thirty-six points protrude, is used. A drop of vaccine is spread thinly on the skin with the edge of the disk and the points of the disk are pressed firmly through the vaccine until the skin is penetrated. A special magnetic holder may be used to facilitate this maneuver, although the palm of the hand is satisfactory. The disk is sterilized after use to be used again. The concentration of freshly made vaccine is 15 mg. per ml.; that of freeze-dried vaccine is 30 to 75 mg. per ml.

Rosenthal needle. The end of a straight sewing-type needle held tangentially, as in the smallpox vaccination, is used to make 3 rows of 10 puncture marks each, all rows to be 4 mm. apart. The vaccine dosage is the same as that for the Rosenthal disk.

Spring-actuated instrument (Birkhaug). A sterilized, thin piece of cellophane or paper is moistened with 20 mg. per ml. of BCG on both sides and

placed on the skin. The headplate of the instrument is then placed over the paper and a trigger is released that allows the needle-plate to enter to a depth of 1 to 3 mm.

Transcutaneous Scarification Method of Negre and Bretey

This consists of placing a drop of vaccine of 15 to 75 mg. per ml. on the skin and making linear scars 1 cm. apart in vertical and horizontal axes of 1 to 4 hatch-like formations. One hatch is made for children, 4 for adults. A vaccine-moistened dressing is then placed over the vaccinated site for twenty-four hours.

Intracutaneous Method

This is performed by making an intradermal skin wheal with 0.1 to 0.15 mg. of vaccine contained within 0.1 ml. of diluent.

The reactions to the multiple puncture method are negligible. The usual reaction in infants is the production of small, pinhead-size papules that appear in ten to twenty days and disappear one to two months later. In adults and children, the lesions are 2 to 3 mm. in diameter; these at first become erythematous and then scaly and finally disappear completely. The intracutaneous method frequently produces local ulcers; occasionally suppurating regional lymph nodes appear within a few weeks or even within three years. Anderson and Palmer[8] point out that although the multiple-puncture method is less innocuous, it produced in one trial only 56 per cent of "takes," whereas the more effective intracutaneous method produced about 82 per cent of "takes."

Mass BCG vaccination has been carried out for some time in France, Norway, Sweden, Denmark, Brazil, Japan, Russia and Canada. The use of BCG is compulsory for certain groups in France, Norway and Brazil. In the United States there has been no mass use of BCG, except that at present the United States Public Health Service has three large mass surveys in progress, but it is too early to evaluate the results. However, since 1947 20,000 persons have been vaccinated in Columbus, Georgia, as well as 6950 in New York State and 3483 in Pennsylvania. Pope[14] stated that by late 1949 about 1400 nurses and medical students in Boston, Massachusetts, would have been vaccinated.

Ferguson[15] in 1946 reported his study made from 1934 to 1943 among nurses of general hospitals and sanatoriums in Canada, which showed an apparent reduction of the tuberculosis morbidity rate of 75 per cent after vaccination. Ferguson discovered that 80 per cent of the entering classes in the schools of nursing were tuberculin negative. His nonvaccinated group consisted of 1368 nurses studied between 1934 and 1938, before BCG vaccination was initiated. In this group the rate of tuberculosis morbidity was 4.02 per cent. The vaccinated group of 1005 nurses, studied from 1938 to 1943, developed a morbidity rate of 0.89 per cent. The average period of observation for both groups was 2.42 years. However, Ferguson admitted that his study had no true controls, in the accepted sense of the word.

Aronson and Palmer[16] found, after a six-year study of 3000 Indians, that vaccination definitely reduced the mortality and morbidity rates of tuberculosis. The Indians were judged to be free of tuberculosis prior to vaccination, as manifested by their failure to react to PPD. The ages varied from one to twenty years, and 1550 were vaccinated with a single dose of either 0.1 or 0.15 mg. of the vaccine. There were 1457 controls who were chosen at random. No changes were made in the living conditions of the persons involved in the study, and all participants were followed by tuberculin tests and x-ray studies. Among the vaccinated group there were 4 deaths due to tuberculosis as compared with 28 deaths from tuberculosis among the controls. The morbidity showed the following comparable figures when the cases were first observed:

Condition	BCG Group		Control Group	
Enlarged hilar glands	21		122	
With parenchymal lesions	13		92	
Without parenchymal lesions	8		30	
Minimal tuberculosis	10		29	
Advanced tuberculosis	1		2	
Extrapulmonary tuberculosis	2		8	
Pleural effusion	6		24	
Total incidence per group	40		185	

In Aronson's first study[16] he failed to mention that he used the alternate case method. However, in a later article[17] covering an eleven-year follow-up study on the same groups of Indians, he mentions that the cases were alternated from the beginning of the study. The follow-up study, made after eleven years, showed that deaths from tuberculosis in the control group numbered 53, in contrast to 6 deaths in the vaccinated group.

Levine and Sackett[18] report a seventeen-year investigation in New York of 2084 children of tuberculous families. During the last eleven years of this study alternate case methods were used. The mortality ratio before alternation of cases was 3 in the vaccinated and 18 in the nonvaccinated groups; after alternation of cases, the mortality was 8 in both groups. However, during the first seven years of their study, there was a tendency for the physician to vaccinate the children of the more intelligent and co-operative parents.

Levine's latest report[19] is a thirteen-to-twenty-four-year follow-up study of 1165 adolescent children, of whom 601 had been vaccinated with BCG during infancy. The remainder were controls. Chest x-ray films were taken and follow-up studies made in only 550 subjects, of which 298 had been vaccinated. The vaccinated group revealed 3 cases with x-ray evidence of healed primary complex and 2 cases of reinfection tuberculosis. Twenty-seven of the nonvaccinated group of 286 had x-ray evidence

of a healed primary complex and no cases of reinfection tuberculosis. There were no deaths due to tuberculosis in either group. Levine concludes that BCG vaccination can prevent a primary pulmonary tuberculosis complex during the period of post-vaccination tuberculin allergy.

Rosenthal's[20] study of 2831 Chicago newborn infants living under the poorest conditions showed the tuberculosis mortality to be reduced among the vaccinated group by 85.7 per cent. There was 1 death in the vaccinated group in contrast to 7 in the nonvaccinated group. Rosenthal fails to mention, however, how his controls were selected. He also reported that a positive tuberculin reaction was present six years later in 80 per cent of the children vaccinated at birth. Of further interest, 88.6 per cent of Chicago student nurses, who were vaccinated, had positive Mantoux tests three years later.

Kinney[21] presented 2 cases of student nurses in whom tuberculosis developed twenty-seven and twenty-eight months after vaccination. Both had explosive onsets of tuberculosis after four to six weeks' exposure on the tuberculosis wards. The predominant feature was the mediastinal-lymph-node involvement and the lack of generalized systemic reactions. At the end of two years there was no evidence of any calcification in 1 of the 2 student nurses, and Kinney concluded that BCG vaccination seemed to modify the course of reinfection tuberculosis and produced atypical cases.

Another study of BCG vaccination is Vorwald's[22] work on the guinea pig. The BCG-vaccinated guinea pigs, who were later exposed to silica dust, died of progressive disese. When the tubercle bacilli from the progressive lesions were injected into healthy guinea pigs, only the usual localized lesions occurred.

Gedde-Dahl[23] states that to study the effect of BCG on tuberculosis morbidity involves a long delay but if the early manifestations, such as pleurisy and erythema nodosum, have been reduced, one might draw some prior conclusions about the effect of vaccination. Mass vaccination was done in Norway during the years 1947 and 1948, but one must not forget that since 1943 mass tuberculosis surveys with x-ray, case finding and isolation have been carried out, — which will influence the morbidity rate. Of the following figures, the incidence of those vaccinated with BCG is not known.

Year	Erythema Nodosum	Pleurisy
1941	1,374	2,989
1942	1,416	2,687
1943	1,155	2,203
1944	1,192	2,293
1945	1,073	2,108
1946	1,147	1,991
1947	859	1,708
1948	634	1,247

In Iceland, from 1930 to 1945, without the use of BCG, there has been a precipitous decline in tuberculosis mortality — from 200 per 100,000 to 70 per 100,000 persons. Thus, the Scandinavian results are not wholly due to BCG vaccination alone but also reflect the effects of better tuberculosis control.

Since BCG is relatively unstable, much research has been done on freeze-dried vaccine and the even newer irradiated vaccine. Sarber and his associates[24] reported the preparation of a virulent human strain of tubercle bacilli that was rendered nonviable by ultraviolet irradiation. This vaccine had antigenic properties equal to BCG on the basis of guinea-pig protection tests, and on gross examination produced no tuberculosis or minimal infection in over 50 per cent of the animals. However, its period of stability was measured in months as compared with days for BCG vaccine.

Another type recently developed is the Vole bacillus. Wells[25] showed that when the Vole bacillus, a murine type of tubercle bacillus, was injected even in large doses under or into the skin, it did not produce progressive disease. A control group of 91 subjects selected at random had a tuberculosis morbidity rate 7.3 times greater than the vaccinated group of 81 persons.

As Dubos,[5] Anderson and Palmer[6] and Dickey[26] separately point out, most of the favorable studies have not been made on alternate cases, and the European and foreign reports are far from being controlled studies. Levine and others[27] and Levine and Sackett[18] have reported studies that were controlled by alternate case methods and have shown that the efficacy of BCG really can be questioned, as their control group showed nearly the same tuberculosis morbidity rate as their vaccinated group.

The widespread use of BCG would destroy also the value of the tuberculin test as an item in differential diagnosis or as a screen test in case finding among children and young adults. According to some authorities, the tuberculin reaction following BCG vaccination cannot be distinguished from that of natural infection. In many of the Middle Western schools, less than 10 per cent of the children are tuberculin positive, which reflects the excellence of present methods of tuberculosis control. Dickey[26] points out that in Chinatown, in San Francisco, California, the incidence of tuberculosis infection among Chinese children was 40 per cent in 1930. From 1939 to 1940, 27 per cent of Chinese children were tuberculin positive, and from 1945-1946 only 5 per cent were tuberculin positive. He further states that the mortality rate from tuberculosis among nonvaccinated children in New York City is far better than that of the vaccinated children of Gothenberg, who were exposed to tuberculosis because of poor control of active cases.

It can be easily perceived that BCG is a poor substitute for the time-proved methods of tuberculosis control that have given the United States an enviable record. The favorable reports of BCG are more than matched by ours, without exposure of subjects to subclinical tuberculosis. It is emphasized

again that we must not stop using our best control methods, — those of case finding and isolation, — in favor of the unpredictable BCG. If BCG is used, we must still endeavor to follow our usual tuberculosis-control methods.

In conclusion, as Dubos[5] and Anderson and Palmer[6] have said, the controversy over BCG has not been resolved by the research and clinical application it has received in recent years. The primary considerations at present are the technic of standardization, the standardization dose and alternate case studies. The responsibility for these lies in the hands of all those who advocate its use.

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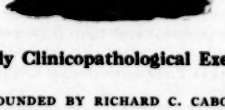
CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 37391

Presentation of Case

A forty-nine-year-old woman entered the hospital complaining of "heart trouble" and "liver pain."

Two years prior to admission she was told that she had diabetes, but she did not take more than small amounts of insulin intermittently. One and a half years before entry she began to have dyspnea. The dyspnea progressed in the next six months until it was present even at rest. At about this time she first noted swelling of the ankles and abdomen and a dull aching pain located above the umbilicus. From this time until admission she led a bed-to chair existence with two- to three-pillow orthopnea. Three and one-half months before entry she was admitted to another hospital, where she remained until admission here. The blood pressure on entry at the other hospital was 230 systolic, 140 diastolic. Two weeks before entry she developed headaches for the first time, and her hands began to swell. Treatment had consisted of oxygen, diuretics, digitalis, a salt-free diabetic diet and repeated thoracenteses.

She was said to have had hypertension for a number of years. A cholecystectomy was performed two years before entry without relief of the abdominal discomfort. There were no other significant past illnesses.

Physical examination here revealed a severely ill, pale, dyspneic woman with cyanosis of the lips and nail beds. There was ++++ pitting edema of the legs and sacrum, with puffiness of the hands and eyelids. The pupils were unequal and unreactive. The fundi showed moderate retinopathy, with scattered flame-shaped hemorrhages and a few cotton-wool exudates. No deep tendon reflexes could be elicited. Sensation was grossly normal. The neck veins were distended 2 cm. above the clavicle in the upright position. There was flatness, decreased breath and voice sounds and decreased fremitus at both lung bases up to the level of the seventh dorsal vertebra. The heart seemed slightly enlarged by percussion, and there was the sugges-

tion of a faint presystolic gallop along the left sternal border but no significant murmurs. The aortic second sound was tambouric. The abdomen showed evidence of considerable ascites, and the liver was definitely enlarged and tender. A mass in the left upper quadrant was believed to be spleen. There was an abscess on the left buttock at the point of intramuscular injections.

The temperature was 99°F., the pulse 90, the respirations 20 and the blood pressure 195 systolic, 100 diastolic.

Urinalysis showed a specific gravity of 1.020, a pH of 5, a ++++ test for albumin and a green sugar reaction; the sediment contained 0 to 3 granular casts per high-power field. Three twenty-four-hour urine specimens contained 12.7, 10.0 and 7.5 gm. of protein. Urine culture grew abundant *B. coli*. The twenty-four-hour urinary sodium excretion was 5.5 milliequiv. per liter. Examination of the blood revealed a white-cell count of 18,000, with 83 per cent neutrophils, and a hemoglobin of 10.5 gm. The blood Hinton test was negative. The serum sodium was 118 milliequiv., the chloride 90 milliequiv., the potassium 5.3 milliequiv. and the carbon dioxide 22.5 milliequiv. per liter; the nonprotein nitrogen was 68 mg., the total protein 3.37 gm., with an albumin-globulin ratio of 1.0, and the fasting blood sugars 92 and 163 mg. per 100 cc. The cholesterol, cholesterol esters and alkaline phosphatase were normal. The prothrombin time was 22 seconds (normal, 17 seconds). The cephalin-flocculation test was negative. A Congo red test showed 80 per cent retention in one hour. A stool guaiac test was +-. Culture of the abscess on the left buttock grew *Staphylococcus aureus*. A chest film made on admission showed fluid in each pleural space, with an increase in prominence of vessels in each lung field, elevation of the left leaf of the diaphragm and bronchiectasis in the right lower lobe. The heart appeared enlarged. An electrocardiogram showed nonspecific T-wave changes.

During her hospital stay the patient was treated with Crysticillin, digitoxin and regular insulin, controlled by urine test, of which she required a total of only 20 units. During the first few days she received hypertonic sodium chloride and albumin intravenously without any benefit. On the ninth hospital day the abscess on the left buttock was incised and drained and subsequently began to clear satisfactorily. On the twelfth hospital day the nonprotein nitrogen was 62 mg. per 100 cc. and the sodium 122.2 milliequiv., the chlorides 95 milliequiv. and the potassium 5.3 milliequiv. per liter. By the twentieth hospital day there was massive edema to the level of the umbilicus, and respiratory embarrassment became more pronounced. On this day a left thoracentesis was performed; 1400 cc. of red to pink fluid was obtained. The fluid had a specific gravity of 1.010 and contained 9000 red cells and 180 white cells (mostly mononuclear) per cu. mm. Cytologic examination of the fluid was negative for tumor cells. The patient's condition slowly worsened, and she died quietly on the twenty-seventh hospital day.

Differential Diagnosis

Dr. Paul Zamecnik*: This patient, I assume, had chronic passive congestion. The dull, aching pain above the umbilicus may have been due to enlargement of the liver. The faint presystolic gallop does not seem significant. It may merely have been related to the hypertension. The cotton-wool exudates may have been associated with malignant hypertension or diabetic retinopathy. In addition, the patient had findings that suggested renal involvement. Since the specific gravity of the urine was 1.020, I assume that the patient did not have a fixed specific gravity but was able to concentrate. I doubt that the protein in the urine would raise the specific gravity that much. The anemia was probably associated with the chronic albuminuria.

May I ask if a glucose-tolerance test was made?

A Physician: No; the 92 mg. of sugar was a fasting sugar, and the 163 mg. was two hours after eating.

Dr. Zamecnik: How long did she have this abscess?

A Physician: It was noted on admission here and was thought to have been produced by previous intramuscular injections. We did not know how many days before admission it had been present.

Dr. Zamecnik: The last sentence in the history does not give a clue concerning whether the patient died in uremia or whether her exitus was more on a cardiac basis. I assume that she probably had nonprotein-nitrogen determinations later than these given in the protocol and that they were not particularly high.

A Physician: They were similar to the one made on admission.

Dr. Zamecnik: The important points in the history suggest that the patient had a steady, slow progression of cardiac and renal impairment, that she had untreated relatively mild diabetes mellitus (at least as far as the insulin requirement was concerned), that she had hypertensive retinopathy and that she had chronic passive congestion on the basis of a myocardial insufficiency. I am led to focus attention on the renal problem and to try to decide whether she was suffering from a primary renal disease or renal disease secondary to something else.

To begin with the second point of view, if the albuminuria was related to chronic passive congestion one would not expect the plasma-protein concentration to have been so low. If the patient had primary renal disease, such as a chronic stage of glomerulonephritis, one might expect more red

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cells, white cells and casts in the urine. Although the triad of albuminuria, hypoproteinemia and generalized anasarca, with enlargement of the liver, would fit in with amyloid disease, the Congo red test is against it and there is nothing else to support it. As for secondary pyelonephritis — again, there is no strong evidence for it, such as cells or casts in the urine.

We are therefore left with the problem of integrating hypertension, retinal disease, diabetes, cardiac failure and renal impairment. I wonder if all these do not fit together in the syndrome that Kimmelstiel and Wilson* described in 1936. They stated that some 20 per cent of diabetics were likely to have a syndrome similar to that present in this case that could be related to intercapillary glomerulosclerosis with damage to the renal glomerular-filtration mechanism.

In summary, I should like to piece the case together in this way: that I am dealing with diabetes mellitus with a generalized arteriosclerosis and arteriolar sclerosis, the Kimmelstiel–Wilson syndrome of intercapillary glomerulosclerosis and coronary arteriosclerosis with myocardial insufficiency.

Dr. Alfred Kranes: Does the presence of the big spleen bother you any?

Dr. Zamecnik: It did; and it does not fit very well with anything but amyloid disease. There were no positive findings suggesting that.

Dr. Kranes: This patient was on the service for quite a while. Aside from being something of a diagnostic problem she was also a complicated nursing problem. Most of the house staff reasoned as Dr. Zamecnik did — that this was a case of Kimmelstiel–Wilson syndrome. What bothered me, although it did not bother many members of the house staff, was the presence of the very large liver and spleen. The size of the liver was rather difficult to estimate because the abdominal wall was quite edematous. There was quite definitely a left-upper-quadrant mass. Although at first we were not in agreement about whether it was spleen or not, as time went on we all believed it to be spleen. If this was primary renal disease, I could not explain why the other two organs were so enlarged. She did not have very much congestive heart failure to account for what seemed to be an enormous liver. I came up with the neat but very illogical explanation that perhaps this woman had a thrombosis of the hepatic vein, the inferior vena cava and so on, thus explaining the whole picture on one basis. However, as a house-staff member pointed out, that would not explain the edema of the hands and face.

Dr. James J. McCort: It seems to me that, if you wanted to know whether the liver and spleen were really enlarged, films of the upper abdomen should have been taken.

*Kimmelstiel, P., and Wilson, C. Intercapillary lesions in glomeruli of kidney. *Am. J. Path.* 12:83-98, 1936.

Dr. Kranes: Not in this case. The technical difficulties were too great to warrant it.

A Physician: Is it possible that the mass in the left upper quadrant was hypernephroma?

Dr. Kranes: We too wondered if what we were feeling was the kidney rather than the spleen. As we could not very well examine this patient by x-ray, the problem boiled down to a discussion of the various personal attitudes toward the mass.

Clinical Diagnoses

Diabetes mellitus.
Generalized anasarca.
?Kimmelstiel–Wilson syndrome.

Dr. Zamecnik's Diagnoses

Diabetes mellitus.
Generalized arterial and arteriolar sclerosis.
Kimmelstiel–Wilson syndrome.
Coronary arteriosclerosis and myocardial insufficiency.

Anatomical Diagnoses

Intercapillary glomerulosclerosis (Kimmelstiel–Wilson syndrome).
Nephrosclerosis, severe.
Lipoid histiocytosis of spleen, marked.
(*Diabetes mellitus.*)

Pathological Discussion

Dr. Tracy B. Mallory: The autopsy showed that the mass in the left upper quadrant was an enlarged spleen, weighing 500 gm., which is about the limit at which a spleen becomes definitely and more or less regularly palpable in our experience. The liver was moderately but not extremely large; it weighed 2020 gm. The heart weighed 420 gm., which for a woman of her size would be a definite hypertrophy. There were no valvular lesions, but the coronary artery showed marked atheromatous deposits, with some points of narrowing but no point of occlusion, and there were no areas of infarction in the myocardium. The kidneys were somewhat small — they weighed 240 gm. — and showed large areas of scarring with thinning of the cortex consistent with either a vascular lesion or the healed stage of a chronic pyelonephritis. I am not aware of any characteristic gross picture for the Kimmelstiel–Wilson lesion, so it became evident that we would have to fall back on the microscopical examination to determine the nature of the renal lesion. We hoped also to help to explain the large size of the spleen, which was definitely bigger than could be accounted for by the simple chronic passive congestion of heart failure.

The typical lesions of intercapillary glomerulosclerosis were found, but in addition there were very marked arteriolar changes and extensive sclerosis of glomeruli, which masked many of the underlying Kimmelstiel–Wilson changes. The spleen was

both interesting and puzzling. There were two well marked areas of infarction, but aside from that throughout all of the splenic tissue were foci of large mononuclear cells of the macrophage type lining the dilated sinusoids and scattered throughout the pulp, which with the usual hematoxylin and eosin stains showed a faintly basophilic and rather hyaline cytoplasm. It was quite unlike anything I could remember having seen before. Dr. Augustin L. Roque has worked very hard at further attempts to characterize these cells, staining them with a battery of lipid stains to ascertain whether they contained much lipoid material. A mixture of several types, — glycerides, cholesterol compounds and phospholipids, — was present in these cells. This does not correspond to any of the lipid-storage diseases, nor does the family history or clinical picture suggest such a possibility; I do not know its significance, but it may be related in some way to the diabetes. I believe the accumulation of lipid-filled cells is sufficiently great to account for the enlargement of the organ that was noted. We found no evidence of amyloid disease.

The adrenal cortex was rather impressively thick, ranging from 2 to 3 mm., which is within the range of what we frequently see in Cushing's disease — although there was nothing else to support such a diagnosis. In fact, Dr. Roque found depletion of the phospholipids and ketosteroids and concluded that there was cytochemical evidence of depressed adrenal secretion.

One surprising finding at autopsy was that there was still a stone of significant size in the common duct. The duct, however, was considerably dilated, and it was quite evident that the stone was not causing any obstruction — at least at the time of death.

DR. ZAMECNIK: Was anything found in the pancreatic islets?

DR. MALLORY: Nothing obvious; there was no hyalinization of the islets of Langerhans.

CASE 37392

PRESENTATION OF CASE

A twenty-nine-year-old woman was admitted to the hospital because of pain in both costovertebral angles.

Ten months before entry the patient first noted dull pain in both costovertebral angles, with frequency, nocturia and turbid urine. She developed fever, shaking chills, nausea and vomiting. *E. coli* was cultured from the urine. Sulfa treatment caused violent nausea and vomiting and was discontinued for this reason; she was treated with penicillin and recovered completely in ten days. She had two subsequent similar attacks, occurring six months and five days before entry. She had noted no renal colic and had not passed blood or stones.

Five years before admission she had a gastrointestinal hemorrhage requiring transfusion, after which x-ray films showed a duodenal ulcer and calcification in the region of both kidneys. Two further hemorrhages occurred three years and three months before entry, each requiring transfusion. For the past five years she had been on a regimen of approximately one quart of milk a day and Amphojel as necessary but no alkali. She fractured a femur at the age of three, requiring open reduction, but there had been no other fractures.

One month before entry laboratory tests revealed that the serum calcium was 10.6 mg., the phosphorus 2.1 mg., the alkaline phosphatase 3.4 units and the total protein 6.5 gm. per 100 cc.; the chloride was 108 milliequiv. per liter and the carbon dioxide 23.4 milliequiv. per liter. The blood pH was 7.33. Examination of the urine revealed a specific gravity of 1.010, a pH of 5.8, a twenty-four-hour calcium excretion of 80 mg., a carbon-dioxide content of 3.6 milliequiv. per liter and no albumin or sugar. The sediment was heavily loaded with white cells and contained an occasional red cell.

Physical examination was negative except for minimal bilateral costovertebral-angle tenderness and a scar on the right thigh.

The urine was acid, had a specific gravity of 1.010 and gave a + test for albumin; the sediment contained a rare red cell and 15 white cells per high-power field. A twenty-four-hour urine specimen contained 47.1 milliequiv. per liter of ammonia and 4.5 milliequiv. of organic acids. Examination of the blood revealed that the hemoglobin was 12.4 gm. and the white-cell count 8300, with a normal differential. The nonprotein nitrogen was 47 mg., the calcium 11.9 mg., the phosphorus 3.9 mg. and the alkaline phosphatase 2.7 units per 100 cc. The nonprotein nitrogen when retested was 29 mg. per 100 cc.; the carbon dioxide and protein were unchanged. Barium-swallow examination showed a slight deviation of the cervical esophagus to the right opposite the level of the first thoracic vertebra (Fig. 1). Extensive nephrocalcinosis was visualized in the medullary portions of the kidneys (Fig. 2). Films of the skull, hands and teeth were not remarkable.

On the sixth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. ALEXANDER LEAF*: One diagnosis that can be made immediately from the excellent studies on this patient is that the patient was on Dr. Albright's service.

May we see the x-ray films?

DR. STANLEY M. WYMAN: The kidneys appear somewhat smaller than usual, and there is a punctate fine stippled calcification in the region of the pyramids (Fig. 2). The bones of the hands show slight

*Clinical and research fellow, Massachusetts General Hospital.

osteoporosis but no other localized changes. The skull and the teeth are not definitely abnormal, and the lamina dura is preserved above the teeth. With barium in the esophagus, the soft-tissue mass in the left lower neck is well seen, displacing the esophagus to the right and posteriorly (Fig. 1).

DR. LEAF: This picture of renal calcification is consistent with nephrocalcinosis, as the record stated. I think the problem here lies in deciding whether the entire picture can be explained by the

FIGURE 1. *Barium-Swallow Film, Showing Deviation of Cervical Esophagus.*

tubular-acidosis type of renal lesion that frequently accompanies this distribution of renal calcification or whether some additional condition must be sought.

It seems to me that there are two distinct types of chronic renal insufficiency. In the usual type that is seen with chronic glomerulonephritis, hypertensive nephrosclerosis, polycystic kidney disease and so forth, the physiologic disturbances that arise result primarily from a diminution in glomerular filtration rate, with ensuing retention of products normally excreted in full or in part. In this group of conditions one usually finds elevation of the nonprotein nitrogen, urea, creatinine, phosphorus, potassium and sulfate concentrations of the blood. There is also retention of organic acids. Substances normally dependent for their excretion largely on the process of glomerular filtration are retained when the filtration rate falls. On the other hand, the calcium level is reduced because of the high serum phosphorus. The serum chloride tends to be normal or low. The acidosis that is characteristic of chronic renal insufficiency is, at least in part, due to retention of acid metabolites within the body.

The abnormal physiology is quite different in the chronic renal insufficiency that accompanies renal tubular insufficiency or acidosis without significant glomerular insufficiency. Renal tubular acidosis has been studied by Albright and his associates,[1] who have pointed out that among the important normal functions of the kidney tubules is the conservation of base, which is accomplished by the production of ammonia and acidification of the

FIGURE 2. *X-Ray Film of Right Kidney, Showing Nephrocalcinosis.*
The left kidney had a similar appearance.

urine. These tubular functions are impaired in this type of renal insufficiency, and the physiologic disturbances one sees are generally caused by impaired tubular function. These cases will show normal serum concentrations of creatinine, nonprotein nitrogen, urea and sulfate, as the filtration rate is not markedly reduced. Because of the inability to conserve base, which is one of the main functions of the kidneys, these patients will con-

tinue to lose cations from the body; one may therefore expect a deficiency of sodium, potassium, calcium and magnesium. One frequently finds the serum potassium to be low. The serum calcium, however, is either normal or low, for the increased loss of calcium through the kidneys will result in a tendency to depression of the serum calcium; this will cause a secondary increase in parathyroid activity, producing a reduction in serum phosphorus level, which stabilizes the serum-calcium concentration. Here one finds a low serum phosphorus, in contrast to the elevated levels in the retention type of renal insufficiency. Also of interest — the serum-chloride levels are characteristically elevated here. The explanation for this is not clear. As the base and bicarbonate are carried out in the urine there is seen a tendency to development of a low total base concentration as well as a low bicarbonate concentration in the extracellular fluid. The usual requirement of preservation of total base concentration results in excretion of an amount of water proportional to the base lost; thus the total base and sodium concentrations show little change, but the serum-chloride concentration must rise as a result of the reduced bicarbonate concentration, and acidosis results. The serum-sodium concentration may be normal or slightly reduced. These patients are frequently dehydrated, and loss of sodium may be associated with loss of extracellular fluid volume without much depression of sodium level.

I want to stress at this point that according to the mechanism just outlined the calcium level may be expected to be normal or low, but I do not see how it could be elevated on the basis of renal tubular acidosis alone.

So much for the two types of chronic renal insufficiency, which I have separated somewhat artificially for the purpose of discussion. Usually renal failure is a combination in varying degree of these two pure types, but sometimes one or the other largely dominates the picture. The case today is an example of a mild but nearly pure case of renal tubular acidosis, as will be indicated.

The etiology of the nephrocalcinosis seen in this case is of interest. For the purpose of this discussion there are two causes of such renal calcification — primary hyperparathyroidism and certain conditions other than hyperparathyroidism, probably largely pyelonephritis. In hyperparathyroidism the excessive excretion of calcium in the urine that occurs over a long period of time, particularly if the patient is ingesting alkali, will result in precipitation of calcium salts within the renal substance. Albright and his co-workers[2] have reported cases of nephrocalcinosis secondary to urinary infection with *H. influenzae*. Thus it is evident that primary pyelonephritis may itself induce this type of renal calcification. When the nephrocalcinosis is the result of hyperparathyroidism secondary infection is very common; hence the presence of pyelonephritis, which our patient definitely had, does not help to distinguish the cause of the nephrocalcinosis.

Review of the laboratory findings in the light of this discussion reveals that most of the findings were in accord with a mild degree of renal tubular acidosis. The serum chloride of 108 was just above normal — in our laboratory 100 to 106 milliequiv. per liter. The carbon-dioxide content of 23.4 milliequiv. was slightly reduced, fitting the elevated serum chloride. The pH of 7.33 indicated slight acidosis. The nonprotein nitrogen was normal, as were the twenty-four-hour urine ammonia and organic-acid excretions. These patients frequently have a high and unexplained organic-acid excretion. The carbon-dioxide content is just twice the value that one obtains by calculation with the Henderson–Hasselbalch equation, in which the known pH of the urine and the normal pCO_2 of the body fluids can be substituted. It cannot be stated whether this is a real discrepancy or only a result of the difficulties inherent in the accurate measurement of low levels of urine total carbon-dioxide content. It is of interest that Latner and Burnard[3] recently reported values of urinary carbon-dioxide content higher than predicted for the observed urinary pH. They believe that failure of the renal tubules to reabsorb bicarbonate is etiologically important in this syndrome of renal tubular acidosis. On one occasion the serum phosphorus was low, in keeping with this picture. The abnormal alkaline phosphatase level and the absence of bone disease in a condition usually characterized by large losses of calcium in the urine indicate only that the dietary intake of calcium was sufficiently high to meet the increased loss, thus preventing dissolution of the bones. The failure to find an elevated urinary calcium excretion on one occasion is most disconcerting, and as it does not fit our picture I shall choose, — judiciously I hope, — to ignore it.

So far everything has fitted the picture of renal tubular acidosis without serious incongruities. Now I come to the serum-calcium values of 10.6 and 11.9 mg. per 100 cc. The latter is a distinctly elevated value, whereas even the former is probably abnormal in view of the average normal value of 9.3 mg. per 100 cc. in our laboratory. As stated above, renal tubular acidosis will not alone cause an elevated serum calcium, and this finding requires an additional explanation — most likely primary hyperparathyroidism.

It thus seems to me that the sequence of events in this case was that of primary hyperparathyroidism producing secondary nephrocalcinosis and renal tubular acidosis with recurrent episodes of bilateral pyelonephritis superimposed. The hyperparathyroidism may have been the result of a solitary adenoma, as suggested by the barium-swallow film, but the possibility of the rarer primary hypertrophy and hyperplasia of all the parathyroids cannot be

excluded. I believe that the operation performed was a parathyroid exploration.

The relation of duodenal ulcer, which this patient had, to primary hyperparathyroidism is interesting. In a series of cases reported from the Mayo Clinic,[4] of 4 patients who had hypertrophy and hyperplasia of the parathyroid, 3 had a history of duodenal ulcer with hemorrhage. In the over-all series, one third of the patients with hyperparathyroidism had histories of duodenal ulcer, and many had had hemorrhages — so the association of these two conditions, whatever its significance, is not uncommon.

DR. TRACY B. MALLORY: I have a question that I should like to ask Dr. Albright. What is your explanation of the mechanism by which renal calcinosis follows pyelonephritis due to *H. influenzae* infection?

DR. FULLER ALBRIGHT: I think that pyelonephritis without hyperparathyroidism can cause nephrocalcinosis in several ways. We have considerable evidence that pyelonephritis leads in some cases to hypercalciuria. This, in turn, could cause nephrocalcinosis, just as does the hypercalciuria of hyperparathyroidism. Furthermore, urea-splitting bacteria may invade the collecting tubules of the kidney and cause an alkaline urine, which would favor precipitation of calcium phosphate and magnesium ammonium phosphate.

CLINICAL DIAGNOSIS

Parathyroid adenoma with hyperparathyroidism.

DR. LEAF'S DIAGNOSES

Hyperparathyroidism with secondary nephrocalcinosis.
Bilateral pyelonephritis.
Duodenal ulcer, with hemorrhage.

ANATOMICAL DIAGNOSIS

Adenoma of parathyroid gland.
(Hyperparathyroidism.)

PATHOLOGICAL DISCUSSION

DR. MALLORY: This patient was operated on with the preoperative diagnosis of an adenoma of the parathyroid gland. A tumor of considerable size, — measuring 8 by 4 by 4 cm. and weighing nearly 4 gm., — was readily found, as would be guessed from the x-ray findings. This was one case in which it was obvious that there was a localized neoplastic process. It is always necessary in these cases to examine all the parathyroid glands at the time of operation, because multiple adenoma, although rare, may be present; about 10 per cent of our cases of hyperparathyroidism show hypertrophy of all the parathyroid tissue. However, in this case a very localized focus was found in one gland, with remnants of normal or slightly atrophic parathyroid tissue surrounding it.

DR. JOHN W. RAKER: There was an additional reason that we did not explore the other side. We found what we took to be a small atrophic parathyroid gland in the region of the thymus on the left side as well. I think it is worth mentioning that this is another case in which the Radiology Department has given us a good lead in the exploration. They have been accurate in many cases in demonstrating some deviation of the esophagus with a barium swallow. This parathyroid adenoma was in the upper parathyroid because its arterial blood supply came from the superior thyroid artery. The atrophied parathyroid gland probably was the lower one. When we had found one large adenoma and one atrophic gland we thought we had excluded primary hyperplasia of the remaining glands. We also thought the adenoma was large enough to account for the quantitative changes in the blood-calcium level and that there was little chance that there was a second adenoma in this instance. The patient developed tetany postoperatively, so presumably she has been cured.

DR. DANIEL S. ELLIS: I should like to ask whether there is regeneration of the tubular damage. Do the kidneys become normal if the primary focus of the disease is removed?

DR. LEAF: I am sure Dr. Albright can answer that better than I can. Once one removes the cause of the primary hyperparathyroidism there may be some passage of stones and a decrease in renal calcification, but I should not expect all kidney function to return.

DR. ALBRIGHT: We have seen cases of nephrocalcinosis due to hyperparathyroidism in which the kidney function gradually improved after removal of the parathyroid adenoma; we have seen other cases in which impaired kidney function progressed after the operation, indicating that irreparable renal damage was present preoperatively.

DR. MALLORY: There is one other x-ray finding that is sometimes seen but was apparently not observed in this case. In some cases the capsule of the tumor has extensive calcium deposits in it. Histologically, we did find some small foci of calcification in the capsule, although it was evidently not sufficient to show up clearly in the x-ray film.

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PHYSICIANS' INCOMES

STATISTICAL evidence is no doubt far more trustworthy than evidence that is not backed up by figures, but it frequently fails to carry conviction. When the results of a joint study by the United States Department of Commerce and the American Medical Association show the average net income (before taxes) of physicians in New England to be $9602, the median being $7818, one may be certain that the reaction of the average physician would be something in the nature of a startled "Who — me?" At the same time he would be cautiously looking over his shoulder to see if anyone were listening, since if he were not making a great deal more (or less) than that, at least the general impression among his friends and patients would certainly be that he was.

The *Journal of the American Medical Association* draws some pertinent conclusions from the published figures in its issue of July 28. The average for the country at large is somewhat higher than that for our local professional colleagues, and in general is about double the figure obtained in a similar survey of incomes in 1929. This percentage increase parallels the general income rise that has occurred in the past twenty years, which, in the opinion of the *Journal's* commentators, shows that both physicians and their patients have been fair with each other, and likewise demonstrates that there has been no general shortage of physicians, since a shortage would have caused their incomes to rise much higher and increases in recent years would have been far greater.

The figures also showed that physicians in the largest cities are not earning the highest average incomes. This should stimulate the tendency, which is already apparent, for well trained young men to establish themselves outside the teaching centers.

Actually, not too much can be concluded from evidence of this sort, but the figures at least are not startling enough to warrant startling conclusions. The medical profession is in about the same position in which it has always been; it is not victimizing the public; it is not in extra short supply. If the next twenty years show no greater changes physicians and public alike should be content.

CONFERENCE ON ALCOHOLISM

WHEN Noah planted a vineyard and became drunk on the wine that he made, and had his nakedness covered by his sons, the world was already old and man's years on it were without number. Wine, too, had been pressed from the grape since 'way back. The first cases of alcoholism recorded in this country were those of two of Leif Ericson's crew who disappeared into the wilderness (presumably somewhere in the neighborhood of Watertown, Massachusetts) and returned some time later in a state of intoxication. Perhaps the head start accounts for Massachusetts's unenviable record of alcoholism.

These are but early instances in the history of alcoholism, a disease of man's weakness that has plagued him since time immemorial. The most encouraging chapter in this history, however, is the latest, which is based on the recognition of alcoholism as a disease rather than as a misdemeanor or even a crime. And disease cannot be successfully treated by the bum's rush or by incarceration in the local calaboose.

Promising efforts are being made, at long last, to consider the alcoholic for what he is and to try to solve his problems in an intelligent and humane manner. In this Commonwealth certain clinics have been operating for some time — notably at the Washingtonian Hospital, an institution devoted entirely to the tteatment of alcoholism, and at the Peter Bent Brigham Hospital, to say nothing of the accomplishments recorded by Alcoholics Anonymous.

The General Court of Massachusetts, also recognizing the pathological significance of alcoholism and the key position of the medical profession in its treatment, a year ago authorized the establishment of a division of alcoholism in the Department of Public Health, under a physician, and the development of a program for the control of the disease. There is sufficient justification for considering this a public-health program.

Aiding all enlightened efforts to solve this problem in an intelligent manner is the Boston Committee on Alcoholism, Incorporated, which is holding its Third Annual Conference on Alcoholism at John Hancock Hall, in Boston, on October 19. This conference, held jointly with the Massachusetts Department of Public Health, is sponsored by the Massachusetts Medical Society, the Massachusetts Psychiatric Society, the Massachusetts Public Health Association, the Visiting Nurses Association of Boston, the churches, the colleges and various groups from business and industry.

The conference will be divided into afternoon and evening sessions, with afternoon panels devoted to education and public health and to medical and community resources. The evening session, including a dinner (no cocktails), will feature industrial programs and alcoholism.

It is expected that the attendance will be even greater than it was at last year's conference, when over 700 persons were registered.

SOUTHWARD THE COURSE OF EMPIRE

Because of the necessity of canceling the joint meeting of the British and South African Medical associations that was to have been held this year in Johannesburg, a physician from the Dominions has for the first time in history been inducted into office in Great Britain as the president of the parent organization. The new incumbent is Dr. A. W. S. Sichel, president of the South African Association, a practicing ophthalmologist of Capetown.

The good feeling that exists throughout this far-flung empire of medicine within the Commonwealth of Nations is an encouraging guarantee of the universal fellowship that persists in the realms of culture, of learning and of service. This was especially brought out, at the meeting of the Association in June, by a gracious duty that devolved upon Dr. Sichel. This was to convey, as president of the Medical Association of South Africa, to himself, as president of the British Medical Association, the cordial greetings of the Medical Association of South Africa—and, as president of the British Medical Association, to offer in return to himself as president of the Medical Association of South Africa "a message of reciprocal greetings to take back to South Africa . . . and better luck on some future occasion."

BLOOD TYPING IN CIVIL DEFENSE

Many lives could be saved in the event of an atomic disaster if both prospective donors and recipients were carrying cards or metal tags giving the blood group and Rh type of each. Universal typing of the whole population, however, is a large task and too expensive to be undertaken lightly. It is important, therefore, to have a large reservoir of donors of known type residing outside probable target areas. Such a project may be quite practicable. In recent months a pilot study has been carried out with funds allocated to the Massachusetts Civil Defense Agency by the Legislature. The early re-

sults of this study are reported in this issue in the column of the Massachusetts Department of Public Health. It is apparent that large numbers of persons can be blood-typed at not too prohibitive a cost. As this study progresses the feasibility of building up the reservoir of donors can be evaluated, as well as the possibility of attacking the problem of typing possible recipients in the target areas. The information gained will be useful in determining how large an appropriation is needed for this purpose.

In normal times it is unwise to accept the results of previous typings. The reliability of the laboratory that performed the test cannot be easily determined. Rechecking should be routine, as well as cross-matching of the bloods of donor and recipient. In an atomic disaster, however, the danger of delaying transfusion may be greater than the possibility of a reaction from incorrect typing, and the precaution may be reasonably omitted, so great is the need for blood and so brief the time available for its preparation and administration. With large numbers of persons being typed today, the physician should search the effects of severely injured persons to determine if a card or tag carrying the information can be found. It is being emphasized that everyone whose type is known should carry the information with him at all times.

Elizabeth Blackwell, the young lady made famous by her perseveringly successful efforts to fit herself for a physician, has finally concluded her studies and opened an office in New York.

Boston M. & S. J., *October 1, 1851*

OBITUARY

ALFRED WORCESTER, 1855-1951

Alfred Worcester died quietly on the afternoon of Tuesday, August 28, some thirty hours after he had sustained symptoms of acute coronary occlusion.

He had been much as his friends had seen him in recent years; he was deeply concerned about world affairs, somewhat lonely for the generation that he and Mrs. Worcester had survived, happy that they could be together as they both lived on, interested in what younger people were thinking and doing, at times a little confused about recent events but perfectly clear about the past and gracious as always, with his kindly sense of humor ever near the surface. His great ability to tell anecdotes was unimpaired — there was never any doubt that it was Alfred Worcester!

In his ninety-seventh year Dr. Worcester looked back over a great expanse; he was six years old at the outbreak of the Civil War; he had heard the story of the Battle of Lexington from the lips of an eyewitness; he had talked with Edward VII and Florence Nightingale (to him she was always "Miss Nightingale"); he knew Osler, although their paths seldom crossed; to him Reginald Heber Fitz was a senior and Harvey Cushing a junior colleague. It

ALFRED WORCESTER, M.D.

was a great era, and in it he identified himself wit the epochal advances of medicine, surgery and ob stetrics (the last he generally referred to as mid wifery). In each of these fields he was a pioneer.

He needed no statistical analysis to be sure tha what he was doing was "significant." The days c discussing whether emetics were of value in th treatment of typhoid fever and other medica small talk were over; there were bigger issues to b faced before the close of the nineteenth century His medical and surgical achievements need no be recounted here, — they were well recognize in his lifetime, — but if he could have read th press notices of his death Dr. Worcester woul again have pointed out that the first *clean* appe dectomy was not performed by himself, for at th time he lay at home convalescing from his own a tack of general peritonitis, but by Edward I Cutler of Waltham. Dr. Cutler operated on o of Dr. Worcester's patients within forty-eight hou of the onset of symptoms, and it was the splend

recovery of that patient that led Dr. Worcester into his vigorous crusade for the surgical treatment of acute appendicitis. There were other crusades — for the cesarean operation, for early hospitalization and rehabilitation of patients with tuberculosis and for the establishment of district nursing as an ancillary form of medical care.

For decades now his accomplishments have been accepted as medical history, fully acknowledged by the Cushings, the Kellys and the Cabots, and recorded in his own expressive style. His writings seemed motivated by an altruism such as rarely flows from the pen of medical authors. The titles of his papers indicated his concern for the patient — "The Care of the Helpless," "The Care of the Aged," "The Care of the Dying," for example. He had something of Franklin's ability to declare himself concisely. "Harbors," he said, "are made safe for mariners not by records of prosperous voyages, but by buoying the dangerous reefs and sunken ledges that have caused disasters." "Physicians alone have the opportunity to bring about this improvement." "There is a special Providence for those who would be gently led." "Undoubtedly there is a larger supply of latent willingness to help the helpless than has yet been brought into action."

A funeral is always a meeting place for a special group; no two are alike. At Christ Church in Waltham, on a hot August afternoon, there assembled the unique group that represented Alfred Worcester. There were doctors, of course; they were not in formal delegations, but the Massachusetts Medical Society and the *New England Journal of Medicine* and other groups that he had served so long and with such distinction were represented. There were nurses, for many of whom he had been a direct link with Florence Nightingale. There were older citizens of Waltham whom he had delivered, and younger ones who would have known him as boys and girls. There were neighbors. There were laborers, politicians, teachers, lawyers, businessmen, farmers, clerks and city officials. They had each lost a great friend. Massachusetts had lost a great physician.

Elizabeth Joy Worcester, 1854–1951

Six days after the passing of Alfred Worcester, death came to his wife, Elizabeth Joy (Hill) Worcester, at their home in Waltham.

Time dealt kindly with this couple; two persons were never more dependent on each other, or more miraculously spared to help each other over a span of sixty-five years. To their relatives, their friends, their neighbors and their fellow-townsmen, it was a fitting and appropriate close of life for a prophet and prophetess who *were* honored in their home town, for the simple reason that they never sought greener pastures.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATHS

Bartlett — Percy Bartlett, M.D., of Hanover, died on July 6. He was in his eighty-first year.

Dr. Bartlett received his degree from Dartmouth Medical School in 1900. He was a member of the American College of Surgeons.

His widow and a daughter survive.

Brown — Hubert L. Brown, M.D., of Hinsdale, died on June 24. He was in his seventy-sixth year.

Dr. Brown received his degree from Baltimore Medical College in 1903. He was a fellow of the American Medical Association.

A son and two daughters survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

A PILOT MASS BLOOD-TYPING PROGRAM

A pilot mass blood-typing program has been conducted this summer by the Massachusetts Civil Defense Agency under the technical supervision of the Diagnostic Laboratory of the Massachusetts Department of Public Health. Because the need for blood transfusions to save the lives of the injured would be tremendous in the event of an atomic disaster, the Blood Section of the Civil Defense Agency, headed by physicians thoroughly familiar with blood-transfusion problems, urged such a project. The purpose of the program was to ascertain the cost and feasibility of mass typing and at the same time to type as many persons as the limited funds appropriated would permit.

The teams have concentrated first on industrial establishments, because it was believed that employees could most easily be organized into smooth-flowing lines, with a minimum of wasted time for the blood typing teams. The teams have worked purposely outside or at the periphery of the target areas because it was thought that increasing the potential donor supply of areas unlikely to be devastated by an atomic attack was an important measure for assuring a supply of blood for the stricken areas. The Boston team has accordingly operated in industrial plants — mainly in Brockton, Whitman, Bridgewater, Randolph and Waltham. The employees of some State offices have also been typed. The Amherst team has worked in Greenfield, Turners Falls, Amherst, Millers Falls, Easthampton, Orange and Athol.

During the first weeks of the project, each test was performed by both tube and slide methods, and read by at least two of the technicians. This double check was considered of the utmost importance in appraising the accuracy of the blood-

typing team. Actually, in the 3100 bloods that were typed by both tube and slide tests, no discrepancies were detected in the ABO grouping, and only three were found in the Rh system. Having gone through this preliminary-double checking period, with an unexpectedly high degree of accuracy for a mass typing program, the teams now perform the slide test only and consequently are able to complete a larger number of tests per day. According to the present procedure, each team can type ten persons every twelve to fifteen minutes. The bloods are obtained by finger stabbing only and are tested, ten at a time, on a single large slide mounted on a special viewing box. The results are read by one laboratory worker while another stamps the results on the identification cards. The tests are then reread by a third worker, and each reading is checked with the type actually recorded on the blood-type identification card.

A sample of the blood-type identification card is reproduced below. Many persons wish to have their religion indicated on the identification card for use in case of emergency; (P) signifies Protestant, (RC) Roman Catholic and (H) Hebrew.

ROBERT A. MACCREADY, M.D.
Assistant Director in Charge
Diagnostic Laboratory

The Commonwealth of Massachusetts
EXECUTIVE DEPARTMENT
CIVIL DEFENSE AGENCY

BLOOD TYPE IDENTIFICATION

DOE, Jane GROUP A
------ Street RH D-POS
City or Town, Mass. (P)
Checked

KEEP THIS CARD WITH YOU

NOTICES

CONFERENCE ON ALCOHOLISM

The third annual Conference on Alcoholism will be held on Friday, October 19, in the Dorothy Quincy Suite, John Hancock Hall, Boston, from 2 to 10 p.m. The conference, to be held under the joint auspices of the Boston Committee on Alcoholism and the Massachusetts Department of Public Health, will this year feature "Public Health and Alcoholism."

Dinner, including registration, is $3; registration to attend sessions only, $1. For reservations address Boston Committee on Alcoholism, Room 525, 419 Boylston Street, Boston, or telephone KEnmore 6-1954.

JOINT MEETING OF THE NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS AND THE HARVARD MEDICAL SOCIETY

The New England Society of Anesthesiologists and the Harvard Medical Society will hold a joint meeting in Amphitheatre D of the Harvard Medical School on Tuesday, October 9, at 8 p.m., Dr. Henry K. Beecher presiding.

PROGRAM

Some Problems of Anesthesia. Henry K. Beecher, M.D.
Clinical Significance of Postoperative Changes in Permeability of Cells to Cations. Francis D. Moore, M.D.
Adrenal Stimulation and Replacement Therapy in Surgery. David M. Hume, M.D.
Abnormalities of Nutrition and Their Correction. Fredrick Stare, M.D.
Psychiatric Risks Involved in Surgical Care. Lincoln D. Clark, M.D.

SPRINGFIELD HOSPITAL

The educational program of the Springfield Hospital for the month of October is as follows:

Wednesday, October 3.
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

Saturday, October 6.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Surgical Conference in the Staff Conference Room.
11 a.m.–12 m. Combined Medical-Surgical Grand Rounds in the Staff Conference Room.

Wednesday, October 10.
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

Thursday, October 11.
12:15 p.m. Staff Meeting in the Staff Room.

Saturday, October 13.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Surgical Conference in the Staff Conference Room.
11 a.m.–12 m. Clinicopathological Conference in the Staff Conference Room.

Tuesday, October 16.
8:30 p.m. Guest Speaker Conference in the Staff Conference Room (speaker to be announced).

Wednesday, October 17.
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

Saturday, October 20.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Surgical Conference in the Staff Conference Room.
11 a.m.–12 m. Medical-Death Review in the Staff Conference Room.

Wednesday, October 24.
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.
12 m.–2 p.m. Pediatric Conference in the Staff Conference Room.

Saturday, October 27.
9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Surgical Conference in the Staff Conference Room.
11 a.m.–12 m. Surgical-Death Review in the Staff Conference Room.

Wednesday, October 31.
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 30–OCTOBER 2. New Hampshire Medical Society. Annual Meeting. Equinox House, Manchester, Vermont.
OCTOBER 3–31. Springfield Hospital. Notice above.
OCTOBER 9. Springfield Academy of Medicine. Page 350, issue of August 30.
OCTOBER 9. Joint Meeting of the New England Society of Anesthesiologists and the Harvard Medical Society. Notice above.
OCTOBER 10. Northeastern New York Radiological Society. University Club, Albany, New York.
OCTOBER 11. The Treatment of Migraine. Dr. John R. Graham. Pentucket Association of Physicians, 8:30 p.m. Haverhill.
OCTOBER 17. Middlesex South District Medical Society. Page 440 issue of September 13.
OCTOBER 19. Conference on Alcoholism. Notice above.

(Notices concluded on page xvii)